BIOPHARMACEUTICS AND RELEVANT PHARMACOKINETICS

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WITH A SPECIAL CHAPTER ON 'QUALITY CONTROL'

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FIRST EDITION 1971

DRUG INTELLIGENCE PUBLICATIONS, HAMILTON, ILLINOIS 62341

CHAPTER 11

Methods of Determining Disintegration Time in Vitro and in Vivo

Methods of Determining Disintegration Time in Vitro

ONE OLD METHOD DEPENDED UPON A WEIGHTED WIRE cutting through a tablet after the latter had been softened in water maintained at 18-20° (Berry, 1939). The first official method described in *Pharmacopoeia Helvetica V* (1934) involved placing the tablet in a 100 ml Erlenmeyer flask, adding 50 ml of water at 37°C and shaking periodically; the maximum disintegration time permitted was 15 minutes. Many different types of disintegration apparatus and fluids have been employed in determining the disintegration time of enteric coated tablets (Wagner, 1956). Many methods have involved the production of some reasonably constant intensity of agitation, and the time required for the tablet to break into fragments small enough to pass through a

screen of stated mesh size is called the disintegration time. The methods official in *U.S.P. XIV* through *U.S.P. XVII* have been of this type and are discussed in detail below. A recent Japanese thermal analysis method provides a measure of not only disintegration time but the surface area generated with respect to time. Several applications of the thermal analysis method have been described (Nakai and Kubo, 1960, Nakai, 1960; Nogami *et al.*, 1967).

The tablet disintegration apparatus which has been official in *U.S.P. IX* through *U.S.P. XVII* was described in detail in *U.S.P. XIV*. The following is taken directly from *U.S.P. XIV* pp. 700-702.

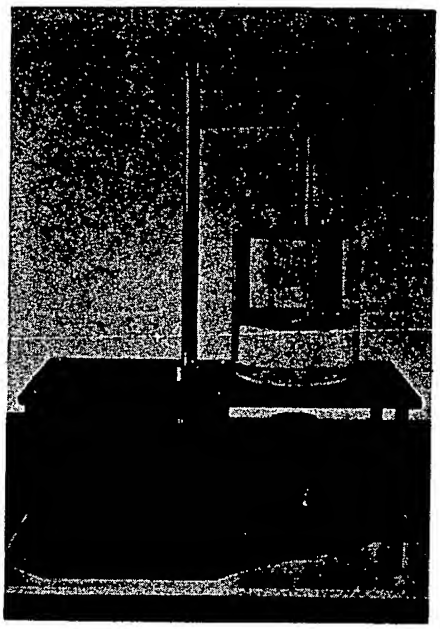
APPLICATION—The *Disintegration Test for Tablets* applies only to uncoated, compressed, or molded tablets having diameters of 15 mm. or less. It does not apply to tablets which are used as troches or to tablets which are to be chewed.

TEST APPARATUS—The test apparatus (Fig. 11.1) consists of a basket-rack assembly (Fig. 11.2), a 1-liter beaker, a micro burner or other suitable heating device, and an electric motor fitted with suitable speed reduction and other gears. A rheostat may also be employed to aid in controlling the number of revolutions per minute.

BASKET-RACK ASSEMBLY—The basket-rack assembly consists of 2 plastic disks about 9 cm. in diameter and 6 mm. in thickness, with six concentrically arranged holes each about 24 mm., in diameter, and capable of receiving glass tubes with an outside diameter of about 23.5 mm. The inside diameters of the glass tubes are approximately 21.5 mm. and the lengths are 7.75 cm. ± 0.25 cm. The tubes are spaced by the plate perforations and held in place by a 10-mesh No. 23 (0.025 inch) W. and M. gauge woven stainless steel wire cloth attached by screws to the under surface of the lower plastic disk. The positions of the glass tubes and the upper plastic plate are further secured and made rigid by means of a stainless steel plate, about 9 cm. in diameter and 1 mm. in thickness, and with 6 perforations each about 20 mm. in diameter, which must coincide with those of the upper plastic plate and the upper open ends of the glass tubes. A central shaft about 8 cm. in length, the upper end of which terminates in an eye through which a string or wire may be inserted, is attached to the stainless steel plate. The parts of the apparatus are assembled, and then made rigid by means of three bolts passing through the 2 plastic plates and the steel plate.

The design described for the basket-rack assembly may be varied in certain details provided the specifications for the glass tubes and the screen mesh size are observed.

THE TEST—Assemble the apparatus and adjust the speed of the motor and the length of the stroke so that the basket moves up and down at a rate of not less than 28 and not more than 32 complete cycles per minute through a distance of not less than 5 and not more than 6 cm. Adjust the level of the water in the beaker so that at the highest point of the upward stroke the wire mesh remains at least 2.5 cm. below the surface of the water and descends to not less than 2.5 cm. from the bottom of the beaker on the downward stroke. Heat the water to a temperature of not less than 35° and not more than 39° and maintain it within that range of temperature throughout the test.



Figue 11.1. Apparatus for USP disintegration test for tablets

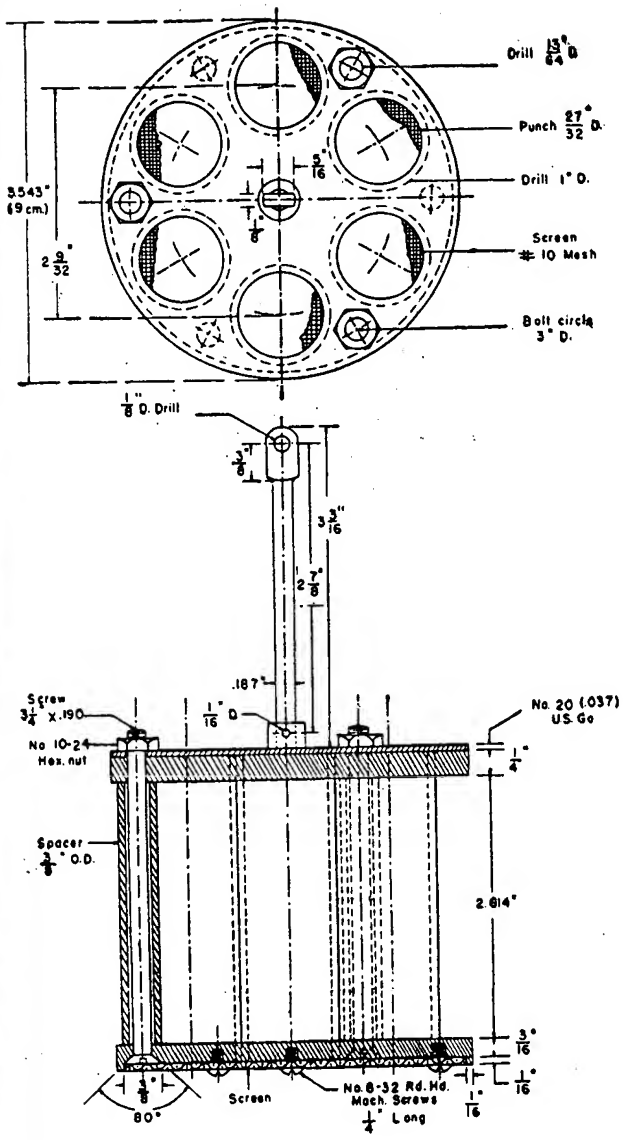


Figure 11.2. Basket-rack-assembly (below) and plastic disc (above) for disintegration test for tablets

Select 6 compressed, uncoated tablets at random from the sample and place one in each of the tubes. Set the basket in motion and observe the condition of the tablets at the end of the prescribed test period by lifting the basket from the water and noting whether or not any tablet parts remain on the screen. The tablets are completely disintegrated when substantially no residue remains on the screen.

It should be noted that *U.S.P. XIV*, which was official from November 1, 1950 to December 14, 1955, described a disintegration test for only uncoated tablets and that the end-point was when "the tablets are completely disintegrated." That is "when substantially no residue remains on the screen." In *U.S.P. XV*, official from December 15, 1955 to September 30, 1960, the description of the disintegration test for uncoated tablets stated, "the tablets are disintegrated if substantially no residue remains on the screen or if any residue that remains is a soft mass having no palpably firm core." It is the opinion of the author that addition of the latter statement made the end-point of the official disintegration test extremely "fuzzy" and was a step backward in that it effectively loosened official standards. In *U.S.P. XV* there were also described disintegration tests for coated tablets, enteric coated tablets and buccal and sublingual tablets. The following is taken directly from *U.S.P. XV*, pp. 937-8.

UNCOATED TABLETS—Place 1 tablet of a sample to be tested in each of the 6 tubes of the basket, and operate the apparatus using water maintained at 37 ± 2° as the immersion fluid unless otherwise indicated in the individual monograph. At the end of the time specified, lift the basket from the fluid to permit observation of the tablets: the tablets are disintegrated if substantially no residue remains on the screen or if any residue that remains is a soft mass having no palpably firm core.

COATED TABLETS—Unless otherwise specified, apply the test for *Uncoated Tablets* except that, if desired, the basket may be immersed in water at room temperature for 5 minutes, with the apparatus in operation, in order to wash off any soluble, external coating. Then expose the tablets for 1 hour to simulated gastric fluid T.S. followed by exposure to simulated intestinal fluid T.S. up to an over-all limit on the time specified for uncoated tablets plus 60 minutes: all 6 tablets are dissolved or softened so that any residue remaining on the screen is a soft mass having no palpably firm core.

ENTERIC-COATED TABLETS—Apply the test for *Uncoated Tablets* except that if desired the basket may be immersed in water at room temperature for five minutes, with the apparatus in operation, in order to wash off any soluble external coating. Then immerse the basket containing the tablets, in simulated gastric fluid T.S. maintained at 37 ± 2°, operate the apparatus for 1 hour, and observe the condition of the tablets: the tablets show no distinct evidence of dissolution or disintegration. If one or more of the tablets have partially dissolved or disintegrated, subject additional tablets to the test: not more than 10 percent of the total number of tablets treated show distinct evidence of dissolution or disintegration.

Replace the simulated gastric fluid with simulated intestinal fluid T.S., and operate the apparatus for 4 hours at 37 ± 2° using 6 tablets that have withstood exposure to simulated gastric fluid T.S. for 1 hour. Lift the basket from the fluid, and observe the condition of the tablets: the coatings of all 6 tablets have

broken and the contents have dissolved or softened to the extent that any residue, other than coating shells, remaining on the screen of the basket is a soft mass having no palpably firm core.

BUCCAL AND SUBLINGUAL TABLETS—Apply the test for *Uncoated Tablets* but observe the tablets at the end of the minimum time specified in the individual monograph: All of the tablets are intact except for slight erosion of the surface. Continue the operation of the apparatus until the over-all elapsed time of immersion in the fluid amounts to the maximum time specified in the individual monograph: any residue remaining on the screen is entirely soft.

In *U.S.P. XVI*, official from October 1, 1960 to August 31, 1965, it was stated: "Disintegration time limits are not specified for capsules, since the shell dissolves rapidly in the gastrointestinal tract. Capsules that have been treated to resist solution in the gastric fluid should meet the requirements for disintegration of enteric-coated tablets." It should be noted that because gelatin capsule shells do dissolve rapidly in the acidic stomach fluids is no reason for omitting a disintegration test for capsules. Enteric coatings dissolve in fluids in the *p*H range 5 to 8, as in the small intestinal tract, yet enteric coated tablets have to pass an official disintegration test. Recent work has suggested there should be a rate of dissolution test for many official capsules.

U.S.P. XVI, official from October 1, 1960 to August 31, 1965, further eased disintegration standards for many tablets by introducing disks into the official test procedure. The same disintegration apparatus was employed but the test for uncoated tablets, plain coated tablets and enteric-coated tablets was modified by placing a slotted and perforated cylindrical disk on top of each tablet in the glass tube. The discs provided a rubbing action on the tablet. The following is an excerpt from *U.S.P. XVI*.

*Disks**—Each tube is provided with a slotted and perforated cylindrical disk 9.5 ± 0.15 mm. thick and 20.7 ± 0.15 mm. in diameter. The disk is made of a suitable, transparent plastic material having a specific gravity of between 1.18 and 1.20. Five 2-mm. holes extended between the ends of the cylinder, one of the holes being through the cylinder axis and the others parallel with it equally spaced on a 6-mm radius from it. Equally spaced on the sides of the cylinder are four notches that form V-shaped planes so arranged that their edges are uniformly 2.55 mm. from the cylinder's surface. Each notch creates a 1.60 mm. square opening on the end of the cylinder to be placed downward in the tube and widens to 8.5 mm. on the top of the cylinder along a chord of the top surface. All surfaces of the disk are smooth.

Procedure—

UNCOATED TABLETS—Place 1 tablet in each of the six tubes of the basket, add a disk to each tube, and operate the apparatus, using water maintained at 37 ± 2° as the immersion fluid unless another fluid is specified in the individual monograph. At the end of the time limit specified in the monograph, lift the basket from the fluid, and observe the tablets: all of the tablets have disintegrated completely. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not less than 16 of the total of 18 tablets tested disintegrate completely.

PLAIN COATED TABLETS—Place 1 tablet in each of the six tubes of the basket and, if desired immerse the latter in water at room temperature for 5 minutes to wash off any soluble, external coating. Then add a disk to each tube, and operate the apparatus, using simulated gastric fluid T.S. maintained at 37 ± 2° as the immersion fluid. After 30 minutes, lift the basket from the fluid, and observe the tablets. If the tablets have not disintegrated completely substitute simulated intestinal fluid T.S. maintained at 37 ± 2° as the immersion fluid, and continue the test for a total period of time, including previous exposure to water and simulated gastric fluid T.S., equal to the time limit specified in the individual monograph plus 30 minutes, lift the basket from the fluid, and observe the tablets: all of the tablets have disintegrated completely. If one or two tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not less than 16 of the total of 18 tablets tested disintegrate completely.

ENTERIC-COATED TABLETS—Place 1 tablet in each of the six tubes of the basket and, if desired, immerse the latter in water at room temperature for 5 minutes to wash off any soluble, external coating. Then operate the apparatus, using simulated gastric fluid T.S. maintained at 37 ± 2° as the immersion fluid. One hour later, lift the basket from the fluid, and observe the tablets: the tablets show no distinct evidence of dissolution or disintegration. Then add a disk to each tube, and operate the apparatus, using simulated intestinal fluid T.S. maintained at 37 ± 2° as the immersion fluid, for a period of time equal to 2 hours plus the time limit specified in the individual monograph, or, where only an enteric-coated tablet is recognized, for only the time limit specified in the monograph. Lift the basket from the fluid, and observe the tablets: all of the tablets disintegrate completely. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not less than 16 of the total of 18 tablets tested disintegrate completely.

BUCCAL TABLETS—Apply the test for *Uncoated Tablets*, but omit the use of the disks, and substitute water as the immersion fluid throughout the test. After 4 hours, lift the basket from the fluid, and observe the tablets: all of the tablets have disintegrated.

SUBLINGUAL TABLETS—Apply the test for *Uncoated Tablets* but omit the use of the disks, and substitute water as the immersion fluid. Observe the tablets within the same time limit specified in the individual monograph: all of the tablets have disintegrated.

*Disks meeting these specifications are obtainable from McKenzie and Company Inc. P. O. Box 604, Pittsfield, Massachusetts.

U.S.P. XVII, official from September 1, 1965 to sometime in 1970, describes the same disintegration tests as in *U.S.P. XVI* above. Kaplan and Kish (1962) suggested a gasket insert modification of the U.S.P. tablet disintegration apparatus in which a thin, flexible rubber gasket is placed in the bottom of the glass tubes in contact with the lower stainless steel wire cloth. This obviates the use of disks in the apparatus in most cases. The rotating bottle method of Souder and Ellenbogen (1958) was also used to test disintegration of pelleted preparations.

Although only a general impression which cannot be proved, the author believes that the easing of disintegration standards in the *U.S.P.* contributed to later problems which several companies had when they found tablets they were selling were not fully available physiologically. During the early clinical testing period the tablets studied were probably quite acceptable and

provided the desired clinical response for the dose administered. As the official disintegration test standards eased, as indicated above first by introducing a "fuzzy" end-point then by introducing disks, the companies eased their own standards in controlling some products. This later got the companies into difficulties when more stringent and exacting criteria became commonplace such as blood level and urinary excretion studies.

Composition of Disintegration Test Media Used in in Vitro Tests

Uncoated tablets (*i.e.*, conventional compressed tablets) have usually been tested in either water or simulated gastric fluid. Enteric coated tablets and plain coated tablets, such as sugar-coated tablets or non-enteric film-coated tablets, have usually been tested first by exposure to simulated gastric fluid then by exposure to simulated intestinal fluid. A wide variety of simulated gastric and intestinal fluids have been described in the literature, for example, by Toplis (1915), Wruble (1930) and several pharmacopeias of the world.

The research leading to the quantitative correlation of *in vitro* with *in vivo* disintegration times of enteric coated tablets described by Wagner *et al.* (1958) was carried out before simulated intestinal fluid *U.S.P. XV* became official. The artificial fluid, *p*H 6.9, used in these studies had the following composition:

Pancreatin U.S.P.	10 Gm
Ox Bile Extract U.S.P.	4 Gm
M/5 Potassium biphosphate	250 ml
M/5 Sodium hydroxide	140 ml (or sufficient)
Deionized water, q.s. to	1000 ml.

The simulated gastric fluid, T. S., which has been official in *U.S.P. XV* through *U.S.P. XVII*, has the following composition:

Sodium chloride	2.0 Gm
Pepsin	3.2 Gm
Hydrochloric acid	7.0 ml
Water, q.s. to	1000 ml

This test solution has a *p*H of 1.2.

Simulated intestinal fluid, T.S. *U.S.P. XV* was directed to be prepared as follows: "Dissolve 3.48 Gm of monobasic potassium phosphate in water to make 100 ml, and mix 25 ml of the resulting solution with 190 ml of 0.02N sodium hydroxide and 400 ml of water. Add 10 Gm of pancreatin, mix, and adjust the resulting solution with 0.2 N sodium hydroxide to *p*H of 7.5 ± 0.1. Add sufficient water to make 1000 ml."

Simulated intestinal fluid, T. S. *U.S.P. XVI* and *U.S.P. XVII* was directed to be prepared as follows: "Dissolve 6.8. Gm of monobasic potassium phosphate in 250 ml of water, mix, and add 190 ml of 0.2 N sodium hydroxide and 400 ml of water. Add 10 Gm of pancreatin, mix, and adjust the resulting solution with 0.2 N sodium hydroxide to a *p*H of 7.5 ± 0.1. Add water to make 1000 ml."

Many laboratories carry out combined disintegration and rate of dissolution tests on tablets and capsules using automated equipment in which the test solution is passed through a flow cell and the amount of drug in solution is determined by a spectrophotometric procedure. In these tests one cannot use pepsin in the simulated gastric fluid nor pancreatin in the simulated intestinal fluid since they will interfere in the spectrophotometric procedures. Sometimes, in such equipment, the U.S.P. fluids without the pepsin and pancreatin are employed in the tests. In other cases simple buffer solutions and 0.1 N hydrochloric acid are employed.

Methods of Determining Disintegration in Vivo

Several different methods have been studied over the past 40 years to determine disintegration *in vivo*. Most of the methods arose in studies pertaining to the evaluation of enteric coated tablets but some of the methods were subsequently applied to the evaluation of simple uncoated compressed tablets and plain coated tablets. The methods are as follows:

1. Tablets containing calcium sulfide leading to eructation of hydrogen sulfide.
2. Visualization of barium sulfate by means of fluoroscopy or roentgenography.
3. Urinary excretion of methylene blue and salicylate.
4. Physiological availability method based on urinary excretion
5. Blood level measurements.
6. Saliva test for iodide following administration of potassium iodide in tablet form.
7. Yo-yo method: withdrawal of the tablets by means of a string attached to them.
8. Visualization by means of the gastroscope or fiberscope.
9. Induced vomiting
10. Radiochemical method.

Wruble (1930) administered enteric coated tablets containing calcium sulfide and methylene blue to human subjects. If the tablet was inadequately coated and disintegrated in the stomach it was thought that the subject would eructate hydrogen sulfide gas. If the tablet disintegrated in the intestine the methylene blue would be absorbed and be excreted in the urine which would be visualized by its blue color. Commenting on Wruble's use of calcium sulfide, Bukey and Bliven (1936), administered ½ grain *sugar-coated* calcium sulfide tablets to 41 subjects. Only 9 subjects (22 percent) reported eructation of hydrogen sulfide gas and they concluded: "This shows conclusively that an enteric-coated tablet containing calcium sulfide might disintegrate in the stomach without protection of eructation." It should be pointed out that there was the possibility that the sugar-coated tablets did not disintegrate in the stomach contents either; this was just assumed by Bukey and Bliven.

The most common method of determining disintegration time *in vivo* has been using a radio-opaque substance, usually barium sulfate, and visualizing the tablets in the gastrointestinal tract of human subjects

by means of x-rays. Both fluoroscopy and roentgenography have been used. The method was introduced by Losinski and Diver (1933) and used by many subsequent investigators including Bukey and Biven (1936), Crane and Wruble (1938), Selye (1946), Feinblatt and Ferguson (1956), Wagner *et al.* (1958, 1960), Gruber *et al.* (1958), Lachman (1964), Steinberg *et al.* (1965) and Merenda and Green (1966). If the subjects are exposed to the x-rays at frequent enough time intervals a reasonably accurate estimate of the stomach residence time and the time required for disintegration of an enteric-coated tablet in the small intestine may be made. In the case of uncoated dosage forms the disintegration time in stomach fluids may be estimated reasonably well. For example, Wagner *et al.* (1960) tested unprotected pill starters containing barium sulfate both *in vitro* and *in vivo*. *In vitro* in both simulated gastric fluid U.S.P. and simulated intestinal fluid U.S.P., the pill starters completely disintegrated to a fine powder in one minute. When approximately 300 pill starters were administered in a No. 3 gelatin capsule to a starved dog on two different occasions the capsule shell had been broken and the pill starters had completely disintegrated between 1¾ and 5 minutes after ingestion in one trial and between 1 and 2½ minutes after ingestion in the second trial.

Urinary excretion of such tracer substances as methylene blue (Wruble, 1930) and salicylate (Losinski and Diver, 1933) provides some information that the dosage form administered has disintegrated. But due to the lag in urinary excretion and difficulties in assaying very low urine levels at very early times post ingestion as well as the pharmacokinetic problem of interpreting the data no good estimates of disintegration time *in vivo* may be obtained, in general, by this method.

The physiological availability method employing urinary excretion (Oser *et al.*, 1945) compares the total amount of drug excreted in the urine following the test preparation to the total amounted of drug excreted in the urine following administration of the drug orally in a readily available form such as an aqueous solution. The method provides excellent estimates of relative adsorption of a drug but provides no information concerning the exact time of disintegration of the dosage form *in vivo*.

Blood level measurements have been used as an index of disintegration *in vivo* by several investigators. The lag time between time of ingestion of the dosage form and the time when the whole blood, plasma on serum concentration, time curve begins to rise has been employed as an index of disintegration time *in vivo* for uncoated preparations. The method has been applied by Boger and Beatty (1950) with procaine penicillin tablets, by Wright *et al.* (1953) with benzathine penicillin G tablets, by Schulert and Weiner (1954) with tablets containing phenylindanedione, by Tarnowski (1957) with shellac-coated PAS granules, by Juncher and Raaschou (1957) with penicillin V tablets, by Clark and Lasagna (1965) with two brands of enteric coated aspirin tablets, by Rasmussen (1966) with enteric coated quinine tablets, and by Jouhar *et al.* with radioactive ^{42}KCl.

Gruber *et al.* (1958) demonstrated the disintegration of enteric compression coated tablets and the dissolution of the core tablets in man by serial roentgenography, by incorporating potassium iodide in the tablets and testing for iodide in saliva and by a "yo-yo" technique in which the tablets were attached to strings and the tablets visualized by x-rays then withdrawn at various times post administration. Steinberg *et al.* (1965) also employed the "yo-yo" technique as well as several others such as induced vomiting, roentgenography, the fiberscope and the biosonar to investigate disintegration of antacid tablets in man. They found that the best method involved preparing 20-30 mesh particles containing barium sulfate then mixing these with the antacid granulation and compressing the mixture into tablets. Disintegration *in vivo* was then followed by means of x-rays.

The radiochemical method is really a variant of the blood level method. Instead of using a microbiological or chemical assay method to detect the drug in blood a radioactive compound is administered in the dosage form and the radioactivity measured in whole blood, plasma or serum at various times post administration. One of the earliest applications involved the use of radioactive sodium chloride. A very slow rise in the radioactivity level in plasma was interpreted as indicative of leakage through the enteric coating while a very rapid rise in the level was interpreted as indicating that the tablet had disintegrated in the intestinal tract. Jouhar *et al.* (1968) used the method to compare release of radioactive ^{42}KCl from a slow release preparation of the coated granule type and from an enteric coated tablet made by directly compressing ^{42}KCl crystals then coating them by the dipping method with a solution of cellulose acetate phthalate and vinyl acetate copolymer. A solution of ^{42}KCl in water was employed as a control in the *in vivo* studies. The release patterns of the slow release and enteric coated tablets *in vivo* were similar except that there was a considerable delay (ca. 3 hours) for the enteric coated tablet before plasma ^{42}K activity was measured. There was no evidence that sudden release and absorption of potassium took place following administration of the enteric coated tablet. The author feels that the latter result was a consequence of the direct compression of the ^{42}KCl crystals to prepare the core tablets. One would expect such a core tablet to be analogous to a constant surface pellet. Experiences of the author in testing enteric coated erythromycin tablets indicates that once the enteric coated tablet did disintegrate *in vivo* the serum concentration of erythromycin rose extremely rapidly provided the tablets were suitably formulated. In the latter case reasonably accurate estimates of the total elapsed time between time of ingestion and the time of disintegration *in vivo* could be made for each subject by determining the lag time between time of ingestion and the time when the serum concentration curve started to rise steeply.

CHAPTER 12

Disintegration of Dosage Forms in Vivo

Miscellaneous In Vivo Studies

THROUGHOUT THE PAST 40 YEARS MANY INVESTIGATORS have observed a qualitative relationship between disintegration times determined *in vitro* and some parameters measured *in vivo*. Wruble (1930, 1935 and 1938) realized that many enteric coatings did not perform their intended function and was one of the first to approach the problem in a scientific manner. The introduction of roentgenoscopy by Losinski and Diver (1933) and of roentgenography by Bukey and Brew (1934) provided very useful tools for determining disintegration *in vivo*. Employing the data of Crane and Wruble (1938), Wagner *et al.* (1960) calculated that 174 tablets freshly coated with ammoniated shellac were emptied from the stomach of human subjects after an average time of 3.61 hours (standard deviation 1.47 hours) and disintegrated in the small intestine after an average time of 2.55 hours (standard deviation 1.08 hours). One lot of tablets coated with ammoniated shellac was tested initially and after storage for one year at room temperature. None of the freshly coated tablets remained intact in the small intestine whereas 7 out of 35, or 20 percent, of the one year stability sample did remain intact in the small intestine. Similarly, Tarnowski (1957) tested shellac-coated granules of p-aminosalicylic acid (PAS) *in vitro* and *in vivo*. One lot of granules initially disintegrated *in vitro* in 15 minutes but the time had increased to 30 minutes after storage for 1½ years. Another lot of gran-

ules initially disintegrated in 11 minutes *in vitro* but after storage of the granules for 3 years the time had increased to > 60 minutes. When blood levels of PAS were measured in three human subjects the freshly coated granules and the granules which had been stored for 1½ years yielded satisfactory blood levels of PAS (6 to 7 mg percent) but a 3½ year-old preparation gave inferior blood levels (< 2 mg percent). It appears obvious that the disintegration time of shellac coated dosage forms increases both *in vitro* and *in vivo* after storage of the dosage forms at room temperature. However, there are suitable enteric coatings whose disintegration characteristics change very little or not at all upon storage at room temperature and examples will be given in a later section.

Selye (1946) reported that two types of coated ammonium chloride tablets he studied give entirely different results both as measured by clinical response and by roentgenography. One, a commercially available but unidentified brand yielded no clinical response in one patient but when the patient was switched to a specially prepared gelatin-coated tablet with a thin resinous film (Dalitol - Frank W. Horner, Ltd., Montreal) the expected clinical response, namely a reduction in CO_2 combining power, was obtained. Roentgenography in 4 subjects showed that the enteric coated tablets tested remained unchanged in the bowel after 2½ hours while the specially coated tablets were not visible and were assumed to have disintegrated within 2 hours. He also pointed out that the specially coated tablets produced gastric discomfort in only 2 of 60 patients. He also suggested that constipation attributed to ammonium chloride may be due to undigested tablets and not due to the drug *per se*.

Boger and Beatty (1950) tested two lots of procaine penicillin tablets. They found that the tablets with a longer disintegration time gave lower, more irregular blood levels that rose more slowly and that much less penicillin was excreted in the urine (about 4 percent) than following tablets which disintegrated more rapidly (30 percent). A study of plasma penicillin concentrations in 18 patients showed that the absorption of procaine penicillin when administered as rapidly disintegrating tablets was little different from absorption following administration of an aqueous suspension of the drug.

Wright *et al.* (1953) showed that substantially lower and more irregular blood levels of penicillin were obtained when benzathine penicillin G was administered orally in tablets with an *in vitro* disintegration time in the range 90-125 minutes than when the drug was given orally in tablets with disintegration time in the range of 30-45 minutes and 10-15 minutes. Failure to demonstrate detectable levels of penicillin at various times after single oral doses of 200,000 units of benzathine penicillin G before breakfast in the three types of tablets studied is shown in Table 12.1.

Schulert and Weiner (1954) studied the anticoagulent phenylindanedione. They stated: "The initial supply of commercial tablets was found to be of two types: one type rapidly disintegrated in water, the other remained as a hard tablet for over 30 minutes after submersion. The former tablet resulted in blood levels similar to those which follow the administration of the drug intravenously or in capsules. The 'hard' tablets, however, were slowly, erratically and incompletely absorbed since plasma level peaks were frequently not achieved for 6 to 12 hours (compared with about 2 hours for capsules), and in some instances only negligible amounts of the drug were detectable in the plasma. . . . The formula responsible for the 'hard' tablets is no longer in use."

Table 12.1. Number of Subjects with Less Than Detectable Penicillin Levels

Designation of Tablets	In vitro Disintegration Time (mins.)*	Hours after dosing 1	2	4	6	8	Total number of entries
Hard	90-125	4	7	9	9	11	40
Intermediate	30-45	0	0	5	6	6	17
Soft	10-15	0	0	4	5	6	15

*Simulated gastric fluid used. (From Wright *et al.*, 1953)

Juncher and Raaschou (1957) showed that the potassium and calcium salts and the free acid of penicillin V dissolve at different rates and that the *in vitro* rates of dissolution correlated with the blood levels of penicillin achieved in man. They also showed that with the most rapidly dissolving form, potassium penicillin V, the availability of the penicillin for absorption can be affected by the processing methods and physical properties of the tablets made from the salt. This is illustrated in Figure 12.1 which shows average penicillin levels of ten fasting subjects following oral administration of 400,000 units of potassium penicillin V in tablets having four different *in vitro* disintegration times.

Swintosky and Blythe (1960) studied relative availability of aspirin from uncoated and enteric coated tablets in a crossover study employing six adult male human subjects. Oral administration in fixed doses (four 333 mg aspirin tablets initially, followed by two 333 mg tablets) at regular time intervals every 6 hours to the 90th hour was continued through a time interval when steady-state absorption-excretion conditions prevailed. No *in vitro* disintegration data were given. The average excretion of salicylate in the urine was essentially the same for the enteric coated and uncoated tablets as shown in Table 12.2 but actually the availability of aspirin from the coated tablet was somewhat less than from the uncoated tablet based on the averages and the ratios shown.

Levy and Hollister (1964) pointed out that the U.S.P. tablet disintegration test not only failed to predict physiological unavailability of an enteric coated aspirin tablet but also failed to discriminate between an available enteric coated sodium salicylate tablet and an unavailable enteric coated aspirin tablet. Both the

Table 12.2. Average Free Salicylate Recovered in the Urine Following Oral Administration of Repetitive Doses of Aspirin in Uncoated and Enteric Coated Tablet Forms

URINARY COLLECTION INTERVAL (HOURS)	AVERAGE FREE SALICYLATE EXCRETED IN URINE		
	UNCOATED TABLET	ENTERIC COATED TABLET	RATIO OF ENTERIC/ UNCOATED
0-12	353	284	0.806
12-24	408	497	1.218
24-36	560	517	0.923
36-48	525	457	0.870
48-60	612	526	0.859
60-72	540	515	0.953
72-84	591	555	0.939
84-96	490	474	0.967
TOTAL	4079	3825	Av. 0.938

Data from Swintosky and Blythe (1960); ratios calculated by the author (J.G.W.)

Table 12.3. Physiologic Availability of Aspirin from Enteric Coated Tablets

SUBJECT	TOTAL SALICYLATE (EXPRESSED AS ASPIRIN) EXCRETED IN URINE AFTER ORAL INGESTION OF 1 GM OF ASPIRIN (MG)		PHYSIOLOGICAL AVAILABILITY (PERCENT)
	SOLUTION[a]	ENTERIC COATED TABLETS[b]	BASED ON 72 HOUR EXCRETION
1	935	0	0
2	928	235	25.
3	878	58	6.6
4	936	954	102.

aDrug dissolved in 200 ml of water with aid of equimolar sodium bicarbonate

bEnseals ASA, 5 Gm, lot 0038-814708 (3 tablets administered) from Levy and Hollister (1964)

Figure 12.1. Average penicillin levels of 10 fasting subjects following oral administration of 400,000 units of potassium penicillin V in tablets having four different *in vitro* disintegration times. Disintegration times of the tablets from the upper curve to the lower curve were 1, 10, 30 and 60 minutes. The penicillin was only about one-half as available for absorption from tablets having a disintegration time of 60 minutes than from those with a disintegration time of 1 or 10 minutes. (from Juncher and Raaschou (1957) with permission of MD Publications, Inc.)

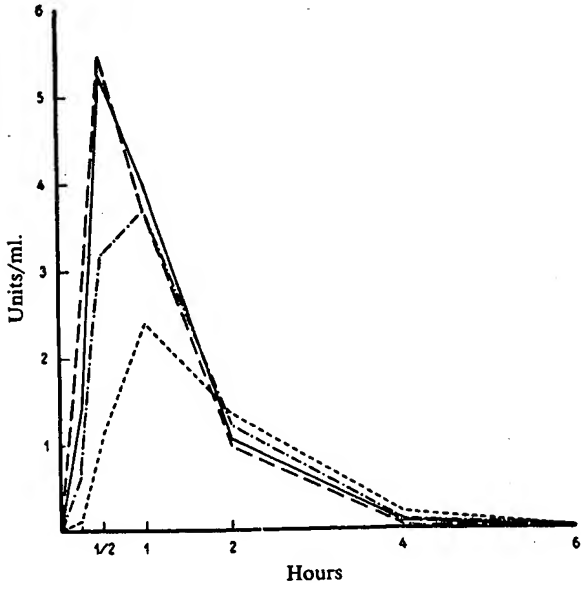


Table 12.4. U.S.P. Disintegration Times of Physiologically Available and Unavailable Enteric Coated Tablets Containing Aspirin or Sodium Salicylate

PREPARATION	U.S.P. DISINTEGRATION TIME (MINUTES)		PHYSIOLOGICAL AVAILABILITY
	AVERAGE	RANGE	
Aspirin Enseals			
Lot 0038-814708	21	18 to 25	–
Sodium Salicylate Enseals			
Lot 8016-816900	19	13 to 25	+
Ecotrin (Aspirin, enteric coated)			
Lot 8936	10.5	6 to 15	+

From Levy and Hollister (1964)

available and unavailable tablets contained the labeled drug content and passed the official U.S.P. disintegration test for enteric coated tablets. Their results are shown in Tables 12.3 and 12.4. It is the author's understanding that subsequent to the work of Levy and Hollister (1964) Enseals ASA have been reformulated and the new product is physiologically available.

Levy and Hollister (1964) pointed out that their results differed from those of Morrison and Campbell (1960) who found that enteric coated aspirin tablets with disintegration times of 111 ± 22.7 minutes were fully available. They stated: "This difference is probably attributable to the varying types of enteric coatings used in different products, with the likelihood that each has its own specific *in vitro* to *in vivo* relationship." This is a significant point and deserves attention.

An enteric film coated tablet of hydrochlorothiazide (50 mg) and potassium chloride (1000 mg) was evaluated by Lachman (1964) in the dog and man as well as *in vitro*. By the U.S.P. XVI procedure the tablets withstood simulated gastric fluid for at least six hours and disintegrated in simulated intestinal fluid in 17-20 minutes. In 9 unanesthetized trained dogs effectiveness of the tablets was demonstrated by the diuresis produced by the hydrochlorothiazide. Serial roentgenograms, and urinary excretion studies in four human subjects showed that the coated tablets resisted stomach conditions and disintegrated in the intestine from three to five hours after oral administration. A diuretic effect was evidenced by a marked increase in urine volume compared with control values.

Leonards and Levy (1965) studied plasma salicylate levels following oral ingestion of 1 Gm of aspirin administered in solution and the same dose administered in the form of a commercially available enteric coated tablet (*Ecotrin*-SKF). Although the physiologic availability of the enteric coated aspirin, as determined by urinary excretion studies, was essentially 100 percent there were marked differences in average plasma salicylate levels following the two forms in 20 subjects. Maximum salicylate levels in plasma (regardless of time of occurrence) averaged 79 mg/L following the aqueous solution and 38 mg/L following the enteric coated tablets. Due to the wide differences in stomach emptying rate of enteric coated tablets from subject-to-subject measured at the same time and for a given subject administered the tablets at different times an average blood level curve obtained following administration of an enteric coated tablet of a drug will almost always look inferior to the average levels obtained following administration of the drug in solution or some other rapidly available form. Even when such comparisons are made on the basis of determination of the area under the plasma concentration curve for each individual subject in a crossover study a problem arises because of the fixed blood sampling schemes which usually must be imposed in these studies. The investigator has no way of knowing when the enteric coated tablet has emptied from the stomach (unless roentgenography is utilized as well) and hence cannot alter his sampling scheme

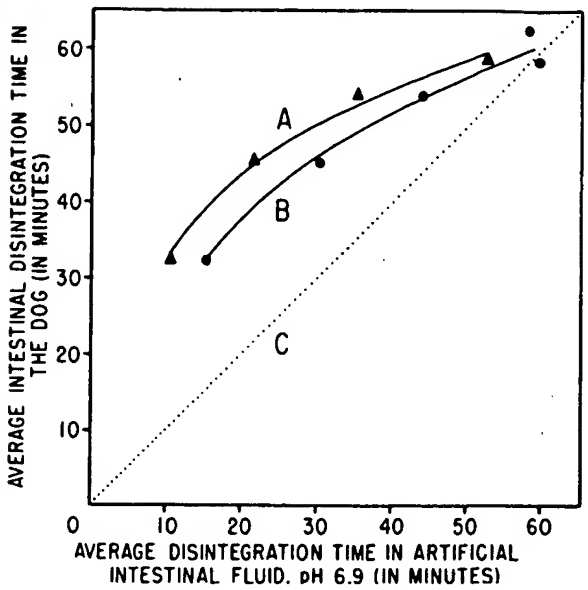


Figure 12.2. Curve "A" is a plot of average intestinal disintegration time in the dog against average disintegration time of the enteric coating (difference between average disintegration time of whole enteric tablet and average distintegration time of subcoated tablet) in artificial intestinal fluid, pH 6.9. Curve "B" is a plot of average intestinal disintegration time in the dog against average disintegration time of the whole enteric coated tablet in artificial intestinal fluid, pH 6.9. Curve "C" represents the results that would be expected if the *in vivo* disintegration time equalled the *in vitro* disintegration time. (From Wagner *et al.*, 1958, with permission of the *Journal of Pharmaceutical Science*)

Table 12.5. Averages Stomach Retention Times of Enteric Coated Tablets in Stomachs of Starved Dogs (from Wagner *et. al.*, 1958)

LOT NO. ENTERIC COATED TABLETS	NO. DOGS	TOTAL NO. OF TESTS[a]	AVERAGE RETENTION TIME IN STOMACH (MINS.) UNADJUSTED[b]	ADJUSTED[c]
I	3	6	98	113
II	3	6	73	88
III	3	6	105	120
IV	3	5	105	107
II*	3	3	108	124

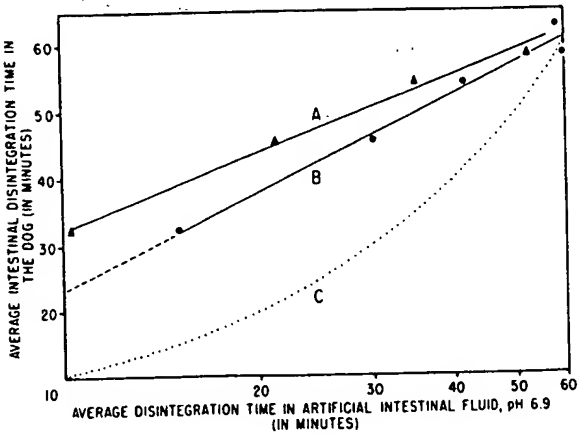
[a]Each test involved 4 enteric coated tablets.

[b]Observed (and unadjusted) averages.

[c]Adjusted averages whch reflect that the dogs were not balanced over the lots.

*Same as lot II except tablets stored in sealed flint glass bottles for one month at 47° C.

Figure 12.3. Curve "A" is a plot of the average intestinal disintegration time in the dog against the logarithm of the average disintegration time of the enteric coaing only in artificial intestinal fluid, pH 6.9. The equation of the "least squares" line is: *in vivo* = 37.6 log *(in vitro)* − 5.3; the correlation coefficient is 0.996 and the standard deviation of scatter is 1.3 minutes. Curve "B" is a plot of average intestinal disintegration time in the dog against the logarithm of the average disintegration time of the whole enteric coated tablet in artificial intestinal fluid, pH 6.9. The equation of the "least squares" line is: *in vivo* = 47.9 log *(in vitro)* − 24.7; the correlation coefficient is 0.989 and the standard deviation of scatter is 2.1 minutes. Curve "C" represents the result that would be expected with this method of plotting if the *in vivo* disingration time equalled the *in vitro* disintegration time (from Wagner *et al.*, 1958, with permission of the *Journal of Pharmaceutical Sciences*)



to suit the particular subject at that particular time. Hence the entire plasma concentration time curve is not well defined for each subject on the enteric coated preparation. Long-term steady state studies such as performed by Swintosky and Blythe (1960) and Clark and Lasagna (1965) obviate many of the single dose study difficulties.

Clark and Lasagna (1965) did perform a long-term steady state study in which plasma concentrations of salicylate were measured after administration of uncoated aspirin and two brands of enteric coated aspirin. The design was such that the order of administration to the same eight patients and two healthy volunteers was as follows.

uncoated aspirin (days 1, 2, and 3)	enteric coated aspirin, brand S (days 4-8)	
uncoated aspirin (days 9 and 10)	enteric coated aspirin, brand L (days 11-15)	uncoated aspirin (day 16)

Brand "S" was *Ecotrin*-SKF and brand "L" was *Enseals* ASA, .3 Gm - Lilly. Satisfactory and reasonally consistent blood concentrations of salicylate were obtained with both the uncoated aspirin tablets and the enteric coated tablets, brand "S". However, they reported that results with brand "L" indicated capricious and generally poor absorption. During the time interval when brand "L" was administered there was an impressive gradual decrease in plasma salicylate concentration. The last measured plasma salicylate concentration of each subject while on brand "L" was in all but one instance the lowest of any of the values recorded for that subject during the entire 18-day study.

Table 12.6. Summary of in Vivo and in Vitro Disintegration Times of Enteric Coated Tablets (from Wagner *et al.*, 1958)

LOT OF ENTERIC COATED TABLETS	INGREDIENTS OF ENTERIC COATING SOLUTION EXCLUDING SOLVENT	AVERAGE WEIGHT APPLIED PER TABLET DURING COATING (MG)		DISINTEGRATION TIME (MINS.)			
		ENTERIC SUBSTANCES ONLY	TALC[a]	IN VITRO[c] AVE.	IN VITRO[c] S.E.[b]	IN VIVO (DOG) AVE.	IN VIVO (DOG) S.E.
I	Styrene-maleic acid copolymer, dibutyl phthalate	25	91	15.1	0.3	32.2	2.6
II	Hydrolyzed Resin SC-2, dibutyl phthalate	15	89	30.1	0.9	45.2	1.7
III	Cellulose acetate phthalate, propylene glycol, Span 80	12	57	43.8	0.6	54.0	3.7
IV	Starch acetate phthalate, propylene glycol, Span 80	21	79	58.1	1.5	62.5	3.9
II*	Same as Lot II except tablets stored in sealed flint glass bottles for one month at 47° C.			59.8	2.2	58.3	7.3

aTalc was used as the dusting powder during application of the coating solution.

bS.E. = Standard error of the average.

cDisintegration time of 12 tablets in simulated intestinal fluid, pH 6.9 at 37° C., using the U.S.P. apparatus. End point taken when 99-100 percent of tablet fragments had passed through the screen. Tablets had been exposed initially for 2 hours to simulated gastric fluid U.S.P. (pH 1.2).

Rasmussen (1966) studied plasma concentrations of quinine following oral ingestion of quinine hydrochloride in aqueous solution, uncoated tablets and from enteric coated tablets as a function of coating thickness. The coating solution for the enteric coated tablets was 200 Gm of cellulose acetate phthalate and 10 Gm of castor oil dissolved in 1790 Gm. of acetone. He found that the rate of absorption and the amount absorbed were the same from the aqueous solution and the uncoated tablets. However, the plasma concentrations following the enteric coated tablets were quite different. With increasing thickness of the enteric coating layer, increased *in vivo* disintegration time was observed. The slow absorption and decrease in amount of quinine absorbed with increasing thickness of the coating were observed both when the dose was given as 10 tablets of 50 mg each and with the dose given as a single coated tablet containing 500 mg. He concluded that "apparently the coated tablets disintegrate in the lower parts of the small intestine where quinine is more slowly and less completely absorbed."

Quantitative Correlations

Correlation of in Vivo with in Vitro Disintegration Times

Apparently the first quantitative correlation of *in vivo* and *in vitro* disintegration times was published by Wagner *et al.* (1958). Subcoated barium sulfate tablets were enteric coated with several different coating solutions. Dogs trained to lie quietly on the x-ray table were used. For those studies directed toward evaluating the stability of the coatings in the stomach the dog was fed 30 minutes prior to administration of four tablets. Under these conditions gastric retention exceeded seven and one-half hours. For the correlation studies the dogs were administered four enteric coated tablets (of the same type at a given time) and, in all except two cases, 50 ml. of 0.1 N hydrochloric acid following an overnight fast. X-ray photographs were taken 45 minutes following administration of the tablets and at intervals of 15 minutes or less thereafter. Both the average stomach retention time and the average disintegration time (from time of emptying into the duodenum to complete disintegration of the tablet in the small intestine) were determined for the four tablets in each test. The average stomach retention times of five lots of enteric coated tablets is shown in Table 12.5.

Table 12.6 summarizes the *in vitro* and *in vivo* disintegration times in simulated intestinal fluid *p*H 6.9 and in the intestine of the starved dog, respectively, for the same lots of enteric coated tablets.

In vitro, the disintegration time of the enteric coating only was estimated by taking the difference between the average disintegration time of 12 enteric coated tablets and the average disintegration time of 12 subcoated tablets. For lots I, II, III, IV, these differences were 10.3, 21.3, 35.0 and 52.4 minutes, respectively.

The above averages are plotted in Figure 12.2 on Cartesian Coordinate paper. The figures themselves in Table 12.6 and Figure 12.2 indicate there is not a direct proportionality between *in vivo* and *in vitro* disintegration times of the enteric coated tablets studied in the dog. Various attempts were made to linearize these data in order to get some insight into the quantitative relationship. When the average *in vivo* disintegration

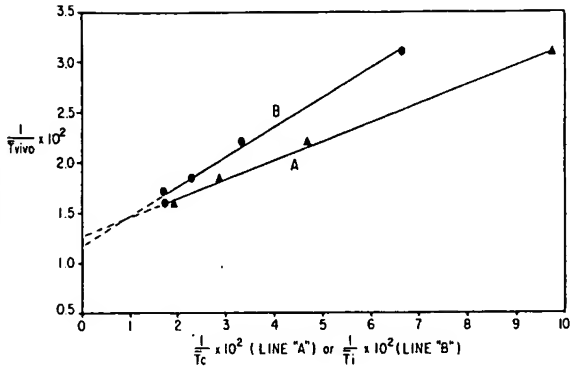
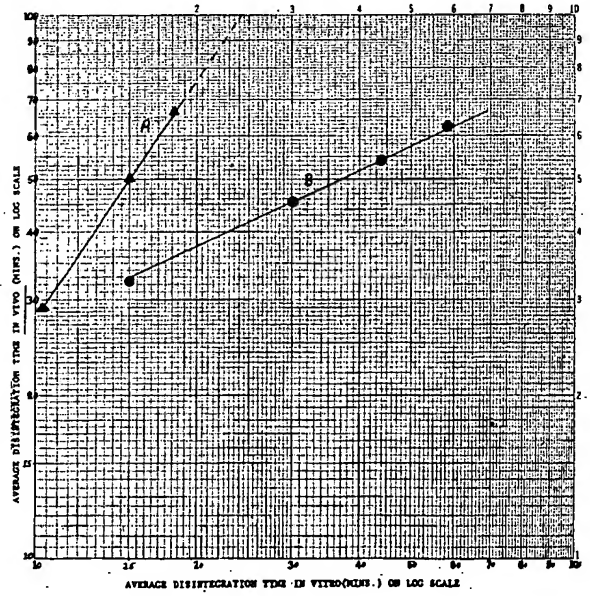


Figure 12.4. Curve "A" is a plot of the reciprocal of the average disintegration time of the enteric coated tablets in the intestine of the dog against the reciprocal of the average disintegration time of the enteric coating only in artificial intestinal fluid, pH 6.9. Curve "B" is a plot of the reciprocal of the average disintegration time of the enteric coated tablet in the intestine of the dog against the reciprocal of the average disintegration time of the whole enteric coated tablet in artificial intestinal fluid pH 6.9. The "least squares" regression lines are : for line "A": $1/T_{vivo} = 0.190\ (1/T_c) + 0.0128$ and for line "B": $1/T_{vivo} = 0.294\ (1/T_i) + 0.0118$. The correlation coefficients were 0.998 for line "A" and 0.996 for line "B" (from Wagner, 1969 with permission of the *Journal of Pharmaceutical Sciences*)

Figure 12.5. Log-log plots of average disintegration time *in vivo versus* average disintegration time *in vitro*. Line A: average disintegration time of compressed tablets in man *versus* average disintegration time of the tablets *in vitro* determined by the U.S.P. XVI procedure in simulated gastric fluid, pH 1.2. Line B: average disintegration time of enteric coated tablets in the intestine of the dog *versus* average disintegration time of the tablets *in vitro* determined in the U.S.P. apparatus without disks at pH 6.9 (after exposure for 2 hours to simulated gastric fluid, pH 1.2). Line A, from data of Steinberg, *et al.* (1965), corresponds to a correlation coefficient of 1.0. Line B, from data of Wagner *et al.* (1958), corresponds to a correlation coefficient of 0.969 ($.05 > p > .02$).



time is plotted against the logarithm of the average *in vitro* disintegration time the data are linearized as shown in Figure 12.3.

Despite the linearization of the data by the type of plots shown in Figure 12.3 this type of plot provides some inconsistencies. Using the regression line for curve "B" of Figure 12.3 namely:

$$\text{In vivo} = 47.9 \log (\text{in vitro}) - 24.7 \qquad \text{Eq. 12.1}$$

We may set *in vivo* = 0 and solve for log (*in vitro*), getting

$$\log (\text{in vitro}) = \frac{24.7}{47.9} = 0.5157 \qquad \text{Eq. 12.2}$$

whence,

$$\text{In vitro} = \text{antilog } 0.5157 = 3.3 \qquad \text{Eq. 12.3}$$

Hence, extrapolation of the least squares line indicates that when the *in vitro* disintegration time is 3.3 minutes the *in vivo* disintegration will be instantaneous and the time equal to zero. Also, extrapolation indicates that when the *in vitro* time is less than 3.3 minutes the *in vivo* disintegration time will be negative.

Another method of linearizing the same data was reported later (Wagner, 1960) and is shown in Figure 12.4. This method of plotting is based on the concept that if the reaction order for the disintegration process is from zero to two then the specific rate constant for the process will be inversely proportional to the disintegration time (*i.e.*, the time required to reach a certain end-point). Hence, the reciprocal, $1/T_{vivo}$ will be directly proportional to the specific rate constant for the *in vivo* disintegration process and the reciprocal, $1/T_c$ or $1/T_i$, will be directly proportional to the specific rate constant for the *in vitro* disintegration process. The problem with this type of plot is that the regression lines did not pass through or near the origin corresponding to $1/T_{vivo} = 0$ when $1/T_i = 0$ or $1/T_c = 0$. In order to estimate the ratio of the specific rate constants for the *in vivo* and *in vitro* processes the line would have to pass through the origin when $1/T_{vivo}$ is plotted *versus* $1/T_i$.

A third way of linearizing the same data is shown in Figure 12.5. This is a log-log plot in which the average intestinal disintegration time in the dog is plotted on a logarithmic scale against the average disintegration time of the whole enteric coated tablet in artificial intestinal fluid *p*H 6.9 on a logarithmic scale. In Figure 12.5 the dog data are plotted and appear as line B which is the same data as plotted in line B of Figures 12.2, 12.3 and 12.4. Line A of Figure 12.5 is derived from the averages reported by Steinberg *et al.* (1965); these authors tested lots of antacid tablets containing pellets of barium sulfate; the *in vitro* disintegration times were determined *in vitro* by the U.S.P. XVI method for uncoated tablets; the *in vivo* disintegration times were determined in man by the roentgenographic procedure. It is of interest that the data of Steinberg *et al.* (1965) is not linearized by the double reciprocal plotting method shown in Figure 12.4 for the dog data but both sets of data are well linearized by the log-log plotting method.

Table 12.7. Comparison of Results Observed in Man, Where Tablets Remained in the Stomach During the Observation Period to *in Vitro* Test in Simulated Gastric Fluid (from Wagner *et al.* 1960)

		IN VIVO RESULTS IN MAN					
TABLET LOT	SUBJECT	NUMBER OF TABLETS	TIME FILM SHOWED INTACT COATINGS (MIN.)	TIME FILM SHOWED COATING BROKEN (MIN.)	IN VITRO TEST[a] AVE	S.E.	COMPARISONS AVE. IN VIVO TIME / AVE. IN VITRO TIME
CI-6[b]	DHG	1	239	327			
	CAS	2	240	329			
	JGW	1	181	241			
	JGW	1	241	311	270	11	307 / 270 = 1.1
				Ave 307			
CI-3[b]	DHG	1	121	180	164	4.7	203 / 164 = 1.2
	CAS	2	120	178			
	CAS	2	210	240			
				Ave 203			
BI-1[c]	DHG	2	300	Not determined	Unaffected after 7.5 hours		> 300 / > 450
	CAS	4	300	Not determined			

[a]Average and standard error to coating broken end-point in simulated gastric fluid U.S.P. (pH 1.2). The coating broken end-point was defined as that end-point when the coating had broken sufficiently so that disintegration or solution of the tablet itself had begun.

[b]Tablets had been enteric coated with styrene-maleic acid copolymer and stored five months at room temperature.

[c]Tablets had been enteric coated with styrene-maleic acid copolymer and stored 12 months at 40° C, then four months at room temperature.

The equation of the log-log regression lines of Figure 12.5 may be written as:

$$\log (\text{in vivo}) = n \cdot \log (\text{in vitro}) + \log Q \qquad \text{Eq. 12.4}$$

Hence, the relationship between the intestinal disintegration time, *in vivo*, and the disintegration time in the laboratory, *in vitro*, may also be written as

$$\text{in vivo} = Q \cdot (\text{in vitro})^n \qquad \text{Eq. 12.5}$$

where Q is the estimated average disintegration time *in vivo* when the *in vitro* disintegration time is unity (one minute) and n is the slope of the log-log line. The Q values for the dog and human data are 0.46 and 1.44, respectively. These values are not directly comparable since the values were derived for disintegration of enteric coated tablets in the dog's intestine and in simulated intestinal fluid, *p*H 6.9, and for disintegration of antacid-barium sulfate tablets in the stomach and intestine of man and in simulated gastric fluid, *p*H 1.2.

In testing some enteric coated tablets *in vitro* and in man Wagner *et al.* (1960) reported the data shown in Table 12.7. These data show a comparison between resistance of enteric coated tablets (coated with styrene-maleic acid copolymer) to the stomach contents of man and resistance of the same tablets to simulated gastric fluid U.S.P. (*p*H 1.2) when tested in the U.S.P. disintegration apparatus. The results suggest that for these enteric coated tablets the U.S.P. test in simulated gastric fluid reasonably predicts the time the tablets will resist stomach contents in man.

CHAPTER 13

Correlation of Physiological Availability of Drugs with in Vitro Disintegration Times

Quantitative Correlations

THESE STUDIES HAVE MAINLY BEEN CARRIED OUT BY SCIentists at the Food and Drug Laboratories, Food and Drug Directorate, Department of National Health and Welfare, Ottawa, Canada. Reviews concerning these investigations have been written by two of the scientists (Morrison and Campbell, 1963 and 1965). In the ten years from 1954 to 1964 scientists of these laboratories published six research papers in which they correlated physiological availability of drugs administered to man in the form of sugar-coated tablets, enteric coated tablets and one triple-dose spaced release preparation with *in vitro* disintegration time (Chapman *et al.*, 1954, 1956; Morrison *et al.*, 1959, 1962; Morrison and Campbell, 1960; Middleton *et al.*, 1964). The work of Chapman *et al.* (1954) was one of the first attempts to correlate *in vitro* findings with quantitative *in vivo* results. This work formed the basis for regulations promulgated in 1957 requiring that in Canada ordinary sugar-coated tablets must disintegrate within 60 minutes *in vitro* in a specified test (Morrison and Campbell, 1965). In their review (Morrison and Campbell 1965) stated: "Despite their weakness, however, disintegration time tests still can provide valuable information on the *in vivo* availability of some drugs" but they also stated: "It is apparent from the foregoing that *in vitro* disintegration tests, as presently used, have certain inherent faults, and eventually must be modified or replaced by more critical tests of physiological availability."

Sodium p-Aminosalicylate in Sugar-Coated Tablets

Figure 13.1 shows the results obtained by Chapman *et al.* (1956) with sugar-coated tablets of sodium *p*-aminosalicylate. In the physiological availability tests sodium *p*-aminosalicylate in both aqueous solution and in hard gelatin capsules was used as control. The average 32-hour excretion by seven subjects follow-

ing the 500 mg test dose was 73.6 mg following the solution and 75.0 mg following the capsule. However for tablets "A" through "G" the average amounts excreted were 73.5, 71.4, 72.7, 73.8, 63.0, 56.9 and 6.6 mg, respectively. Tablets B, E and G were specially prepared by one company to have different disintegration times. Tablets A, C, D and F were marketed products made by four different pharmaceutical manufacturers. Urine collections were made in the intervals 0-2, 2-4, 4-6, 6-8, 8-24 and 24-32 hours post ingestion of the doses. Plots of cumulative percent of the ingested dose excreted *versus* time were quite different for the different sugar-coated tablets. *In vitro* disintegration tests were performed on the same tablets by two different methods. Both methods used the U.S.P. tablet disintegration apparatus. In the Chapman method rubber disks were used and in the U.S.P. method plastic disks were used. In both tests for the first 30 minutes the tablets were exposed to simulated gastric fluid and for the remainder of the time in simulated intestinal fluid. Hence if the tablets had a disintegration time less than 30 minutes they were only exposed to simulated gastric fluid. If the disintegration time was greater than 30 minutes they were exposed to simulated gastric fluid 30 min. and the remainder refers to simulated intestinal fluid. Figure 13.1 is based on the eight and 24 hour excretion values but the data indicate that the asymptotic amounts excreted were not reached for at least 32 hours for all tablets tested.

Table 13.1 gives the average disintegration times determined *in vitro* by both methods and the physiological availability based on 32-hour urinary excretion using 75.0 mg (that excreted after the drug in capsule form) as the denominator in calculating the physiological availability.

Table 13.1. *In vitro* Disintegration Times by Two Methods and Physiological Availability Based on 32-hour Urinary Excretion in Seven Subjects for Sugar-Coated Tablets of Sodium-p-Aminosalicylate (data from Chapman *et al.*, 1956). Tablets are arranged in order of decreasing physiological availability

TABLET LOT	PERCENT AVAILABILITY	AVERAGE IN VITRO DISINTEGRATION TIME (MINS) RUBBER DISKS[a]	PLASTIC DISKS[b]
D	98.4	65.9	63.6
A	98.0	24.0	19.5
C	96.9	61.8	67.1
B	95.2	65.6	58.0
E	84.0	84.4	91.1
F	75.9	76.1	111.5
G	8.8	134.5	200.4

[a] Simulated gastric fluid had a pH of 1.6 and simulated intestinal fluid had a pH of 8.0
[b] Simulated gastric fluid had a pH of 1.2 and simulated intestinal fluid had a pH of 7.5

These data suggest that when the *in vitro* disintegration time is less than about 70 minutes the sodium *p*-aminosalicylate was essentially completely available

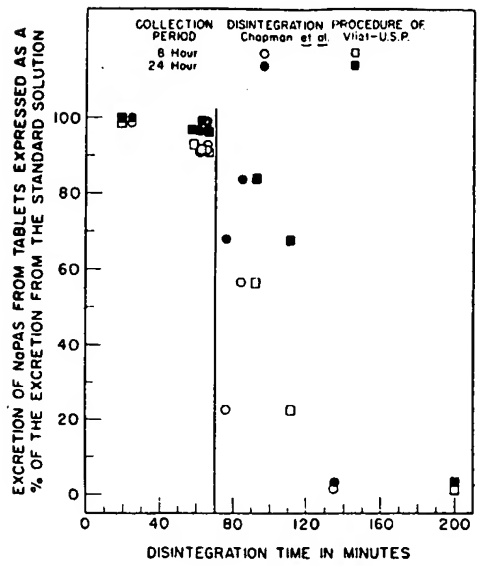


Figure 13.1. Plot of physiological availability of Na PAS from sugar-coated tablets based on 8 hour and 24 hour urinary excretion against the disintegration time of the tablets determined *in vitro* by two different methods (From Chapman *et al.* (1956) with permission of the *Journal of Pharmaceutical Sciences*)

(95-100%) from the sugar-coated tablets. However, when the disintegration time exceeds about 70 minutes by either test method the sodium *p*-aminosalicylate was not fully available and the greater the average disintegration time of the tablets the lower was the physiological availability of the drug from the sugar-coated tablets. The dotted line in Table 13.1 is drawn to show the approximate cut-off point.

Chapman *et al.* (1956) pointed out that particularly for tablet lots E and F the U.S.P. test media and plastic disks were more consistent with the physiological availability figures than the Chapman *in vitro* test employing different fluids and rubber disks.

At the same time that the disintegration test was being performed by the method of Chapman *et al.* (1954) with these sugar-coated sodium *p*-aminosalicylate tablets the authors also measured the amount of drug in solution as a function of time for tablets A,D,E,F and G. From their plots Schroeter *et al.* (1962) estimated the $T_{50\%}$ values (time for 50 percent of the drug to be in solution). The percent availability values are plotted both against the disintegration times and the $T_{50\%}$ values in Figure 13.2. Also plots of $T_{50\%}$ (obtained by method of Chapman *et al.*, 1954) *versus* disintegration time determined by the method of Chapman *et al.* and the U.S.P. XV method plus plastic disks are shown in Figure 13.3. The correlation between $T_{50\%}$ and the disintegration time in the test of Chapman *et al.* for these five lots of sugar-coated Na PAS tablets was highly significant (correlation coefficient of 0.995). In this test, as indicated above, the dissolution rate (reflected by the $T_{50\%}$ value) was determined at the same time as the disintegration time. Schoeter *et al.* (1962) concluded that the disintegration time determined in the test of Chapman *et al.* was truly an indication of the rate of dissolution of sodium *p*-aminosalicylate from the tablets. They also concluded that it was probably for this reason that there was a relationship between the percent availability of the sodium *p*-aminosalicylate in human subjects and the disintegration time of the tablets.

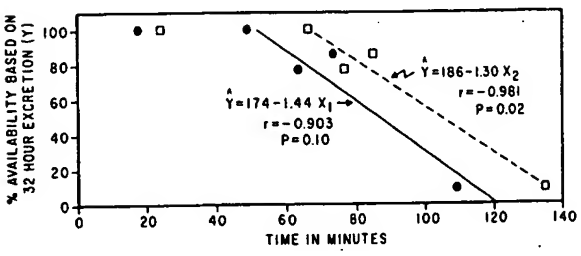


Figure 13.2. Percent availability of sodium p-aminosalicylate from sugar-coated sodium p-aminosalicylate tablets based on 32 hour urinary excretion *versus* □ disintegration time (mins) determined by method of Chapman *et al.* (1954) and ● $T_{50\%}$ (mins) determined at the same time that the disintegration test was carried out. [From Schroeter *et al.* (1962) with permission of the *Journal of Pharmaceutical Sciences*. Original data from Chapman *et al.* (1956)]

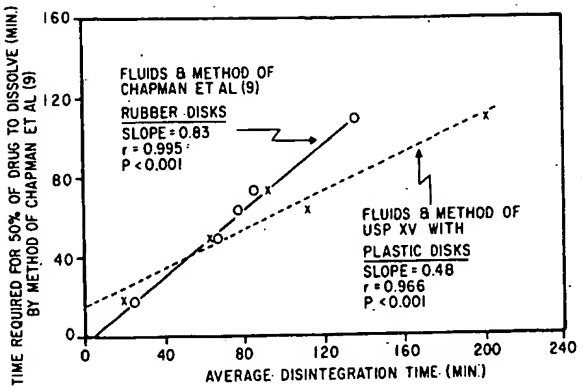


Figure 13.3. Plots of $T_{50\%}$ (time required for 50% of drug to dissolve) by method of Chapman *et al.*, (1954) against average disintegration time determined by two methods. [From Schroeter *et al.* (1956) with permission of the *Journal of Pharmaceutical Sciences*. Original data from Chapman *et al.* (1956)]

Riboflavin, Thiamine and Niacinamide

The relationship between physiological availability of riboflavin in human subjects and *in vitro* disintegration time has been studied by several authors (Chapman *et al.*, 1959; Endicott and Kirchmeyer, 1956; Morrison and Campbell, 1960; Morrison *et al.*, 1962; Ida *et al.*, 1963; and Middleton *et al.*, 1964).

In the physiological availability studies described by Morrison *et al.*, (1959) six to nine normal male subjects, shown to be receiving nutritionally adequate diets, were utilized. While on test, they were allowed to consume their regular meals but were cautioned to refrain from eating foods rich in riboflavin, such as liver, and to eat meals similar in nature from day to day. The subjects were administered doses of 5 mg or 10 mg of riboflavin in a rapidly disintegrating standard tablet, and 3 mg to 10 mg of riboflavin in the form of various sugar-coated tablets. Doses were administered at 8:45 a.m. after breakfast. Urine was collected in opaque bottles containing 2 ml of 3.5 N H_2SO_4 at 2,4,6,8,14 and 24 hours post dosing. Riboflavin in both the tablets and urines was determined by the U.S.P. XV fluorometric procedure. All gross excretion values were corrected by subtracting the appropriate blank determined on the urine of the same subjects without dosing. *In vitro* disintegration times were determined by the U.S.P. XV Second Supplement (1958) method modified by the use of solid or fluted plastic disks. Tablets were immersed for 30 minutes in simulated gastric fluid and the remainder of the time in simulated intestinal fluid as described above. The disintegration time reported was the average of at least two separate tests of six tablets each. The eight commercial products tested were all sugar-coated multivitamin tablets. Products B,C,E,F

and H also contained minerals as well as the vitamins. The mean excretion of riboflavin in five trials conducted over a two-year period following the standard tablet (control) was 58 percent of the dose with a range of 57 to 60 percent. Each trial was based on six to nine subjects. The range in the total of 36 subjects given the standard tablet was from 27 to 78 percent of the test dose. Results obtained by these authors are summarized in Table 13.2.

Table 13.2 *In vitro* Disintegration Times Determined by Two Methods and Physiological Availability of Riboflavin Based on 24-Hour Urinary Excretion from Sugar-Coated Multivitamin Tablets (data of Morrison *et al.*, 1959) (Tablets are arranged in order of decreasing physiological availability)

TABLET	PERCENT AVAILABILITY AVERAGE	RANGE	NO. OF SUBJECTS	AVE. IN VITRO DISINTEGRATION TIME (MINS) SOLID DISKS	FLUTED DISKS
F	81	14-139	7	69	84
A	72	42-103	6	69	—
H	69	21-98	6	62	60
E	51	12-80	7	78	89
G	45	11-92	7	69	61
B	44	18-80	9	75	—
C	24	0-98	7	75	—
D	14	0-53	7	120	—

None of these eight sugar-coated multivitamin products allowed complete availability of the riboflavin they contained. Peak urinary excretion rates of riboflavin were also correlated with the availability values. The average peak excretion rate of riboflavin obtained with the standard tablet preparation was 9.45 μg/min while a minimum average peak excretion rate of only 0.40 μg/min was calculated following oral ingestion of tablet D which had the lowest physiological availability.

Results obtained by Chapman *et al.* (1954) and Morrison *et al.* (1959) are summarized in Figure 13.4 Here the percent availability of riboflavin is plotted against the disintegration time obtained by three different methods. The line drawn at a disintegration time of 60 minutes seemed to reasonably divide the available and not-completely available products and formulations.

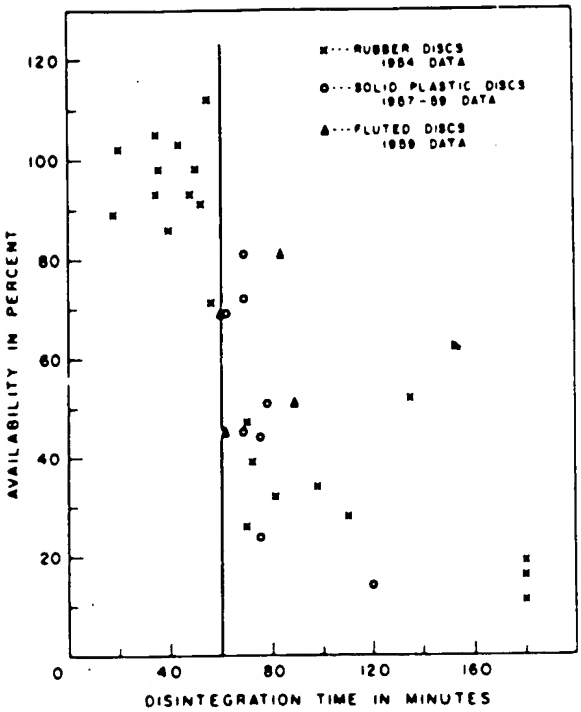


Figure 13.4. Relationship between physiological availability of riboflavin from sugar-coated tablets *versus* disintegration times determined by three different methods. See legend inset at top of figure for key. [From Morrison *et al.* (1959) with permission of the *Journal of Pharmaceutical Sciences*]. Results are summarized in Table 14.3

Table 13.3 *In vitro* Disintegration Times and Physiological Availability of Riboflavin from Enteric Coated Tablets (from Morrison and Campbell, 1960). (Tablets are arranged in order of decreasing physiological availability)

TABLET	PERCENT AVAILABILITY AVERAGE	RANGE	NUMBER SUBJECTS	IN VITRO DISINTEGRATION TIME[a] (MINS) AVERAGE	S.D.[d]
O	81	36-113	5	104[b] (44)[c]	9.7
S	75	33-109	4	80 (20)	6.4
R	41	12-66	6	128 (68)	7.2
T	40	20-72	4	247 (187)	35.6
P	29	0-44	5	241 (181)	58.6

a The apparatus and fluids described in U.S.P. XV and the fluted disks described in U.S.P. XV Second Supplement (1958) were used.

b Tablets were immersed in simulated gastric fluid for 60 minutes and the remainder of the time in simulated intestinal fluid.

c Average disintegration time in simulated intestinal fluid only.

d S.D. = Standard-deviation corresponding to the bracketed average.

Table 13.4. Physiological Availability of Three Vitamins in a "Spaced-Release" Multivitamin Preparation and Its Component Spheres and *in vitro* Disintegration Times (from Morrison *et al.*, 1962)

PREPARATION	AVAILABILITY (PERCENT) RIBOFLAVIN AVE.	RIBOFLAVIN S.E.	THIAMINE AVE.	THIAMINE S.E.	NIACINAMIDE AVE.	NIACINAMIDE S.E.	IN VITRO DISINTEGRATION TIME (MINS) SIMULATED GASTRIC FLUID	SIMULATED INTESTINAL FLUID	TOTAL
Intact Product	38	6.0	43	5.9	64	10.0	—	—	—
Sphere O	77	5.1	98	13.7	122	14.7	25		
Sphere Y	20	1.9	73	11.6	27	6.4	30	57	87
							60	54	114
Sphere R	13	4.5	28	5.0	29	7.8	30	138	168
							60	134	194

It should be noted that Tablets O and T in Table 13.3 were samples from different lots of the same product. Hence the data in Table 13.3 not only showed a reduced availability of riboflavin in all three enteric coated tablets studied but also a marked lot-to-lot variation with two of the three products.

The relationship between *in vitro* disintegration time and *in vivo* release of vitamins from a triple-dose "spaced-release" preparation was studied by Morrison *et al.* (1962). The multivitamin commercial product consisted of three spheres which disintegrated at different times. Sphere O was designed to release the contained vitamins immediately; spheres Y and R were designed to release their contained vitamins approximately three and six hours after ingestion. The three spheres were contained in a gelatin capsule. Each sphere contained labeled amounts of 3.33 mg of thiamine hydrochloride, 1.67 mg of riboflavin and 16.7 mg of niacinamide. Physiological availability values for all three vitamins were determined by the urinary excretion method for the intact preparation and for each of the three spheres using five to seven normal male subjects. Controls were 5 mg of riboflavin or 5 mg of niacinamide administered in rapidly disintegrating tablets and 3.33 mg of thiamine administered in aqueous solution. The availability of thiamine in the intact product was determined by comparing urinary excretion of thiamine after giving the intact product and after giving 10 mg of thiamine in divided doses. The reason for this precaution is that thiamine is absorbed by an active transport process which is saturable. *In vitro* disintegration times were determined with the apparatus and fluids described in U.S.P. XVI including the disks. Results are summarized in Table 13.4.

On the basis of these results Morrison *et al.* stated: "The time limit given in the U.S.P. XVI for plain coated decavitamin tablets is 30 minutes in simulated gastric juice plus 2 hours in simulated intestinal fluid. Sphere R would not pass this test but sphere Y would. The latter sphere, however, showed inadequate availability of all three vitamins tested. It is obvious that riboflavin, thiamine and niacinamide in coated tablets which pass the U.S.P. test may not be fully available to the body. . . . If decavitamin preparations are enteric-coated, the time limit given in U.S.P. XVI is 5 hours (1 hour in simulated gastric juice plus 4 hours in simulated intestinal juice). Sphere R, which would have passed the U.S.P. XVI test, was recovered essentially intact from the feces of human subjects." These results show how difficult, if not impossible, it is to formulate vitamins in sustained-release forms which are fully available to the human body.

Even tablets with very thin coatings and which rapidly disintegrate *in vitro* can show reduced availability of riboflavin as indicated by the work of Ida *et al.* (1963). Compressed tablets containing 9 mg of riboflavin were film-coated by dipping them in: (1) a 10 percent methanolic solution of the copolymer of 2-vinyl-5-ethylpyridine-styrene (VEP-St) or (2) a 10 percent ethanolic-trichloroethane (1:1) solution of the copolymer, 2-vinyl-5-ethylpyridine - methacrylic acid-methacrylate (VEP-MAA-MA). *These tablets disintegrated in water in 4 minutes and disintegrated in simulated gastric fluid in 5-10 minutes by the U.S.P. XVI method.* Uncoated tablets were used as a control. The tablets were tested by the urinary excretion method in 79 men and 52 women in the 18-55-year age range. Results are shown in Table 13.5.

Table 13.5 Mean Amounts of Riboflavin Excreted in Urine in 0-6 Hours After the Test Dose

TABLET	NUMBER SUBJECTS	AVERAGE RIBOFLAVIN EXCRETED (MG) 0-3 HR	3-6 HR	0-6 HR		AVAILABILITY (PERCENT) BASED ON 0-6 HOUR EXCRETION
Uncoated	30	2.512	1.288	3.797	a	
VEP-MAA-MA Coated	51	1.951	1.496	3.447	b	90.8
VEP-St Coated	50	1.251	1.363	2.614		68.9

aAverages are not significantly different ($P > .05$)

bAverages are significantly different ($P \leq .05$)

It is feasible that each type of coating has its own *in vitro-in vivo* relationship and that the 60-minutes time limit imposed by the Food and Drug Directorate in Ottawa, Canada may yield a false sense of security with some products. It should be noted that the results of Ida *et al.* (1963), shown in Table 13.5, were obtained on much larger panels of subjects than in those studies summarized formerly.

In 1964 Middleton *et al.* reported on studies conducted on the relationship between dissolution rate, disintegration time and physiological availability of seven sugar-coated multivitamin products. Dissolution rates and disintegration time were determined with the U.S.P. tablet disintegration apparatus. A close relationship was found between *in vitro* disintegration time and the rate of dissolution ($T_{50\%}$) of riboflavin for the various products as originally pointed out by Schroeter *et al.* (1962). Both the $T_{50\%}$ values and disintegration time correlated reasonably well with physiological availability as measured by urinary excretion of riboflavin. Data is summarized in Table 13.6.

Table 13.6 Physiological Availability of Riboflavin from Seven Sugar-Coated Multivitamin Preparations and *in vitro* Disintegration Times and Rates of Dissolution (Reflected by the $T_{50\%}$ values — Times for 50% of Drug to Dissolve in Fluids During the Disintegration Test). Data of Middleton *et al.* 1964

TABLET	PHYSIOLOGICAL AVAILABILITY (PERCENT) AVERAGE	S.E.	IN VITRO TEST (TIME IN MINUTES) DISINTEGRATION TIME	$T_{50\%}$
G	98	5	20	11
E	94	7	20	11
D	88	11	45	38
B	87	4	45	25
A	58	10	151	114
C	36	10	101	83
F	12	5	98	124

Based on the data shown in Table 13.6 Middleton *et al.* reported a correlation coefficient of 0.923 for the linear regression of $T_{50\%}$ on disintegration time. However, one product, namely F, was quite far off the regression line. They also reported a correlation coefficient of 0.906 for the linear regression of $T_{50\%}$ on physiological availability but two products, F and C, were quite far off the regression line.

Salicylate

The relationship between physiological availability of salicylates from enteric coated tablets and *in vitro* disintegration time was studied by Morrison and Campbell (1960). In four trials with 6 to 9 subjects following test doses of 10 to 15 grains of aspirin *in the form of rapidly disintegrating tablets* the following averages (and range) of salicylate were recovered in the urine: 74.6 percent (59.2-96.2); 86.5 percent (60.4-100.2); 89.2 percent (70.7-98.5); and 87.1 percent (77.4-92.5). Physiological availability from the enteric coated tablets was based on these control values. The results obtained with the seven enteric coated tablets containing either acetylicylic acid, salicylic acid or sodium salicylate (and in some cases also ascorbic acid and/or p-aminobenzoic acid) are shown in Table 13.7.

Table 13.7 Physiological Availability of Salicylate from Seven Enteric Coated Salicylate Tablets and *in vitro* Disintegration Times. Data of Morrison and Campbell (1960)

TABLET	PHYSIOLOGICAL AVAILABILITY AVERAGE	RANGE	IN VITRO DISINTEGRATION TIME (MIN) AVERAGE	STANDARD DEVIATION
G	116	84-136	27	23.1
E	116	84-136	213	21.3
F	107	94-133	145	8.9
D*	101	57-131	110	27.1
B*	95	73-112	86	4.4
A*	87	51-107	87	5.0
C	23[a]	0-90	480*	——

*Tablet A, B and D were samples from different lots of the same product containing only acetylsalicylic acid as active ingredient.

[a]Misleading value since product unavailable to 4 of 7 subjects who took it.

Although all of the tablets tested, except tablet C were fully available none of the enteric coated tablets showed a peak excretion rate of salicylate as high as the standard rapidly disintegrating tablet. The peak excretion rate occurred earlier with the standard than with any of the test preparations studied as would be expected for enteric coated tablets due to stomach emptying rate. Also absorption of aspirin and salicylate from the stomach would be expected in the case of the rapidly disintegrating tablet but not in the case of the enteric coated tablets. The three subjects in whom product C was unavailable recovered the entire 10 tablet doses in their feces. Tablets were recovered in the feces as early as 12 hours after ingestion in one individual, and as late as 72 hours after ingestion in a second subject. A few of the recovered tablets showed cracks in the enteric coating, but all tablets were intact, with only the sugar-coating removed. In a few instances where the tablets had passed through the entire gastrointestinal tract the enteric coating was removed by hand. The cores of the tablets were extremely hard, and even in the absence of the enteric coat, would be expected to resist disintegration for some time.

The difference between the results reported (above) by Morrison and Campbell (1960) and those reported by Levy and Hollister (1964) following a study of enteric coated aspirin and sodium salicylate tablets has been discussed previously in Part II of this section.

Erythromycin

Tablets containing erythromycin which had disintegration times as high as 120 minutes were claimed by

Table 13.8. Blood Levels and Disintegration Times of Erythromycin Preparations (from Endicott and Kirchmeyer, 1956)

ERYTHROMYCIN PREPARATION	DISINTEGRATION TIME (MINUTES) U.S.P. XV METHOD	METHOD A[a]	METHOD B[b]	BLOOD CONCENTRATION[c] (μG/ML) 2 HR	4 HR	6 HR	8 HR
Low Dosage							
Base, specially coated	105-115	95-110	70-80	0	.02	32	.16
Stearate-Sulfa, film-sealed	108-120	69-80	78-83	.04	.16	.16	.04
Base, film sealed	45-52	40-47	38-45	.16	.08	.08	.04
Stearate, film sealed	70-80	66-74	68-76	.32	.08	.04	.02
Stearate suspension	———	———	———	.32	.08	.04	.02
High Dosage							
Base, specially coated	105-115	95-110	70-80	0	1.28	.64	.32
Stearate suspension	———	———	———	2.56	.64	.32	
Base, film sealed	45-52	40-47	38-45	2.56	.64	.32	.16
Stearate, film sealed	70-80	66-74	68-76	2.56	.64	.16	.16
Stearate-Sulfa, film sealed	108-120	69-80	78-83	.64	.64	.32	.08
Base, no coating	10-12	5-10	15-17	.64	.32	.16	.04

[a]For method A see O'Brien *et al.*, *Drug Std.* 23:126, 1955.

[b]For method B see Chapman *et al.*, *J. Am. Pharm. Assoc. Sci. Ed.* 43:297, 1954.

[c]Data originally published by Josselyn *et al.*, *Antibiotics Annual 1954-1955*, p. 279.

Endicott and Kirchmeyer (1956) to yield adequate and effective blood concentration of the antibiotic. These data are shown in Table 13.8.

Specification of a disintegration time limit also involves precise specification of the manner in which the disintegration time is to be determined. An example is the data in Table 13.8 which clearly show that the disintegration times are very much dependent upon the method used to obtain the figures. In eight out of the nine entries in Table 13.8 the method of Chapman *et al.* (1954) gave lower disintegration times than the U.S.P. XV method which was official at that time.

Summary and Discussion

There are some cases where physiological availability and other parameters derived from *in vivo* studies in man correlate well with *in vitro* disintegration time. When the disintegration process is very much slower than the deaggregation, dissolution and absorptive processes then disintegration will be rate-limiting and one might expect a reasonable correlation between disintegration time, measured *in vitro*, and some *in vivo* parameter such as physiological availability. As pointed out by Schroeter *et al.* (1962) and Middleton *et al.* (1964) there is sometimes a high degree of correlation between rate of dissolution (as reflected by the $T_{80\%}$ value) and *in vitro* disintegration time. Hence in these cases either *in vitro* disintegration time or the $T_{80\%}$ values will correlate reasonably well with the physiological availability values. Since disintegration time is the easier control test to carry out it may be used to control the product in those cases where a correlation has been shown. Such correlations have been shown, as indicated above, for three of the water-soluble vitamins with most emphasis on riboflavin, for sodium p-aminosalicylate and for salicylate, all administered as sugar-coated or enteric coated tablets. *This author believes these data should not be extrapolated and applied to all tablets and all drugs.* This author has seen sufficient evidence in the literature and from his own experience to suggest that such *in vitro-in vivo* correlation may apply to several products manufactured by several methods but would not apply to one or more other products containing different pharmaceutical coating agents and adjuvants or containing different drugs.

There are also many cases where measurements made *in vivo* do *not* correlate with disintegration time measured *in vitro*. If dissolution from the agglomerates or granules liberated after disintegration is rate-limiting as is often the case, then one would expect a better correlation between *in vivo* data and *in vitro* rate of dissolution data. Such correlations will be discussed in subsequent sections.

CHAPTER 14

Theory of Tablet Disintegration and Factors Affecting Disintegration Time of Tablets and Capsules

Variables Involved in the Disintegration Test

THE PRINCIPAL VARIABLES ARE:

1. The type of apparatus used. This principally determines the intensity of agitation which, in turn, is affected by the geometry of the system, the rate of flow of the fluids, the presence or absence of turbulence, etc.

2. The composition of the test media or fluids employed. The *p*H, ionic strength, viscosity, surface tension, etc., are all properties determined by the composition of the fluid and each of these properties will affect test results with some or all tablets or capsules.

3. The temperature of the disintegration test fluids. Usually this is held constant at 37°C (body temperature) hence is not a variable.

4. The operator who records the disintegration time. Different people interpret the same test in different ways. For example, Wagner *et al.* (1960) found that two laboratories, "a" and "b", performing the same disintegration test on 49 lots of tablets obtained somewhat different average disintegration times. The results obtained by laboratory "a", namely T_a, and those obtained by laboratory "b", namely T_b, were linearly related such that $T_b = 0.852\ T_a + 4.2$ by the method of least squares.

Variables Involved in the Dosage Forms

As indicated previously, a dosage form of a drug is a drug delivery system and almost anything you do to the system may change the rate of release of the drug from the dosage form. Analogously, almost anything you do in preparing the dosage form may affect its disintegration time. *Some of the important variables in compressed tablet composition and manufacture which affect disintegration time are as follows:*

1. The diluent or filler used to dilute the drug prior to the process of mixing and its concentration relative to the drug.

2. The method of tablet manufacture employed, *i.e.*, whether it is the wet granulation process, the dry granulation process or the direct compaction method. In the wet granulation process the granulating agent or binder and its concentration are important. In the dry granula-

Factors Affecting Disintegration Time of Tablets and Capsules

tion process the compression pressure used to precompress the drug or drug-diluent mixture is important.

3. The granule size and its size distribution.

4. The disintegrant and its concentration and the method of incorporating it.

5. The lubricant and its concentration.

6. Presence or absence of a surfactant and, if present, its nature and concentration and method of incorporating it.

7. The compressional pressure and speed of compression.

8. The drug itself and its properties such as particle size, surface characteristics, solubility, etc.

9. The age of finished tablets and conditions under which they were stored.

Some of the important variables in hard filled capsule composition and manufacture which affect disintegration and deaggregation time are as follows:

1. The drug itself and its properties such as particle size and distribution, surface characteristics, solubility, etc.

2. The method used to reduce bulk in order to encapsulate (*e.g.*, by granulating or slugging).

3. The milling process used to reduce the granules or slugs to a powder suitable for capsulating and the resulting granule size and size distribution.

4. The diluent employed and its concentration.

5. The presence or absence of a surfactant and, if present, its nature and concentration and the method of incorporating it. This is of particular importance with hydrophobic drugs.

6. The nature of the lubricant, its concentration and methods of addition.

7. The "pressure applied" during encapsulating or filling which determines the weight of solids incorporated in a given size capsule shell. For example, hand-filled capsules may have a different disintegration time than machine-filled capsules.

8. The composition and properties of the capsule shell used.

9. The age of the finished capsules and conditions under which they were stored.

Some of the important variables in sugar-coating and enteric-coating which affect disintegration time of the finished tablets are as follows:

1. The type and amount of coating agent applied per tablets.

2. The type and amount of dusting powders applied with the coating solution per tablet.

3. The type and amount of plasticizer and other adjuvants such as surfactants incorporated in the coating solution with the coating agent.

4. The nature and amount of subcoating applied to the compressed tablet before sugar-coating or enteric-coating.

5. The method of applying the coating solution (*e.g.* pan-coating by hand, programmed pan-coating or air-suspension apparatus).

6. The age of the coatings and conditions under which they were stored.

Discussion of Compressed Tablet Manufacture

Compressed tablets today make up the bulk of oral dry product medication. They are popular since: (1) they provide accurate dosage from a chemical analysis view point; (2) they are compact in form and convenient to carry; (3) they provide good stability for most active ingredients; and (4) they are economical to manufacture, which provides a saving for the patient. They have an advantage that they can be made in any shape or size.

The process of mixing involves the blending of the medicament with diluent or filler. The diluent or filler is a harmless substance used to build the size of the tablet to a suitable and convenient size. Usually the medicament must be hand screened, milled or micronized either alone or in conjunction with the diluent, or a part thereof, to achieve a particle size which will bring about uniform mixing. The most common diluents are lactose, sucrose, starch, calcium carbonate, calcium sulfate, etc. Where a colored tablet is desired, the dye is usually added as an ingredient in mixing as a trituration with lactose or starch. It may also be added in solution during the granulation process or as trituration in the lubrication process. The latter method usually leads to mottling unless color is being matched.

The granulation process is the one in which bond is imparted to the mixture and also the characteristics of flowability. After adding the granulating agent to desired wetness, the mass is screened either by hand or by using machinery such as a rotary granulator or an oscillating granulator usually through a 4 to 8 screen. The wet granules are sieved on trays and dried. The dried granules are re-screened to a mesh size of 12-20 depending mainly on the size of the finished tablet and the nature of the dried granules. In some cases granules are prepared from two or more active ingredients then later the granules are blended together. Some of the most commonly used granulating agents are sucrose and glucose solutions, 10 and 20 percent mucilage of acacia, 10 and 20 percent gelatin solution, starch mucilage, starch-sucrose mucilage, and alcohol. In many cases a starch-sucrose mucilage consisting of one part starch, two parts of 50 percent sucrose solution and seven parts of water is satisfactory. Methocel, ethocel or carboxymethylcellulose are often applied as gels with an aqueous base. These can be used to produce films which reduce sensitivity of some active ingredients to chemical reactions through contact with the atmosphere or to reduce interactions between two active ingredients in the formulas. In those cases where active ingredients cannot be subjected to moisture and/or heat, the medicament with diluent, if any, and lubricant are precompressed into slugs. In some cases a dry binder must tbe added before precompression. The slugs are then broken up to the desired mesh size by a machine such as a Stokes oscillator or a Fitzpatrick Homoloid mill. In the direct compaction process crystals or powders are directly compressed into tablets.

During the lubrication process the lubricant and the disintegrating agent, where necessary, are applied to the granules or other stock. A lubricant is a material which will prevent stock from sticking to the punches and dies. In some cases, at moderate concentrations, the lubricant will improve flowability of the granulation.

Some of the more commonly used lubricants are talc, starch, liquid petrolatum, stearic acid, magnesium stearate and calcium stearate. Lubricants should be used sparingly since they markedly affect tablet disintegration and increased amounts will also lead to loss of bond. A disintegrating agent is usually a compound or substance that swells in the presence of water, thus forcing the tablet to break apart when exposed to aqueous media. Starch is still the most comomnly used disintegrating agent. Other disintegrating agents are guar gum, Avicel, Solka Floc Bw-100, Solka Floc Bw-200, Natrasol 250 H and CMC 7HOZP. Several authors have reported that when part of the disintegrant is added prior to wet granulation and the balance is added to the dried sized granules that optimum disintegration results. When a tablet is to be flavored, the bulk of the flavoring ingredients, with the exception of non-volatile sweetening agents, are added during the lubrication process. The flavoring agent may be sprayed on, if an oil, or added as a dry powder. In the past ten years entrapped powder flavors have been exploited to good advantages in making compressed tablets.

The compression process is one of the most important with respect to disintegration time. Using the instrumented rotary tablet press Knoechel *et al.* (1967) have shown that in a certain compressional force region the disintegration time of the finished tablets increases essentially linearly with increase in applied compressional force during compression of the granules or powder. Frequently such increases in disintegration time occur in a region where the tablet hardness (as indicated by hardness testers) is essentially at an asymptotic level. Hence tablet hardness *per se* is not necessarily a good indication of future disintegration test results. One can control compressional pressure within narrow limits with the instrumented rotary tablet machine under production conditions as discussed by Knoechel *et al.* (1967).

Theory of Compressed Tablet Disintegration

It is generally accepted that it is the combined effects exerted by all the factors listed under "Variables Involved in the Dosage Form," as opposed to a single factor in particular, which are responsible for determining rate of disintegration. T. Higuchi and associates demonstrated that the majority of the granules compressed into a tablet retain their individual integrity. Therefore, it may be assumed that disintegration of a tablet takes place in two steps: first, the tablet breaks into granules; second, the granules or fragments break down into smaller particles (Bergman and Bandelin, 1965).

According to Nogami *et al.* (1967) the rate-determining step in tablet disintegration is the process of water penetration into the tablet via the pores. They cautioned, however, that this does not mean that starch

(or other disintegrant) does not affect the process of separation of particles, but they concluded that the separation process will be completed within a much shorter time period than the process of water penetration.

There appear to be two opposing theories concerning the action of starch, as a tablet disintegrant. On the one hand, Ingram and Lowenthal (1966, 1968) observed that swelling of starch grains was in the order of 5 to 10 percent increase in mean grain size and that pepsin and surfactants produced no significant effects on starch grain swelling. Changes in *p*H had little effect on swelling although there was some evidence to show that starch grains swell more at *p*H 5.3 than in lower *p*H media. Ionic concentration *per se* had no effect on swelling but polyvalent cationic salts such as magnesium and aluminum chlorides produced more swelling than monovalent cationic salts such as sodium chloride and sodium sulfate. Analysis of the time effect indicated that swelling of starch grains on exposure to aqueous media occurred apparently instantaneously. They concluded that the increase in volume they observed did not seem of large enough magnitude to cause tablets to rupture. On the other hand, Patel and Hoppenon (1966) found dried cornstarch to increase in volume by 78 percent when suspended in water. They concluded that the primary mechanism in tablet disintegration when starch is used as disintegrant is a swelling action of the starch. They also concluded that capillarity *per se* does not appear to have a disintegrant effect.

Theory applied and developed by Nogami *et al.* (1966, 1967) will be discussed. The penetrating rate of a liquid into a packed powder bed is given by (Peek and McLean, 1934):[1]

$$\frac{dL}{dt} = \frac{r\gamma \cos\Theta}{4\eta L} - \frac{r^2 d'g}{8\eta} \qquad \text{Eq. 14.1}$$

where L is the length penetrated at time t, r is the average radius of void space, Θ is the contact angle between liquid and powder surface, g is the gravitional acceleration constant, and γ,η and d′ are the surface tension, viscosity and specific gravity of liquid, respectively. If measurements are made in a fine powder bed only in the initial period of penetration, the second term on the right hand side of Equation 14.1 can be neglected. Then integrating Equation 14.1, putting $h = o$ at $t = o$ one obtains (Washburn, 1921):[2]

$$L^2 = \left(\frac{r\gamma \cos\Theta}{2\eta}\right) \cdot t = kt \qquad \text{Eq. 14.2}$$

where k is the coefficient of penetration and is equal to the bracketed part. This theory indicates that a plot of L^2 *versus* t will yield a straight line, passing through the origin, with slope equal to k. In many cases the plots conform to theory. In other cases there is curvature and in some cases a lag time before linearity occurs.

It was shown (Nogami *et al.* 1966) that:

$$\log \frac{k}{T} = \alpha - \frac{\beta}{RT} \qquad \text{Eq. 14.3}$$

where T is the absolute temperature, R is the gas constant and β is the apparent activation energy of wetting. They obtained a linear plot of log k/T *versus* 1/T for water penetrating into a bed of potato starch; the β value obtained was 1.67 kcal. For water penetrating a bed of magnesium oxide β values of 2.6, 3.7 and 4.8 kcal were obtained for initial moisture contents of 0, 5.73 and 8.36 percent, respectively.

Assuming: (1) the water-solid interfacial area in the disintegrating tablet, S, increases directly with the length of the capillary void, L, then

$$S = fL \qquad \text{Eq. 14.4}$$

where f is a constant characteristic of the tablet. S reaches a certain value, S_D, at the disintegration time t_D. Substituting for L in Equation 14.2 from Equation 14.4 and rearrangement yields:

$$\frac{1}{t_D} = \left(\frac{f^2}{S^2{}_D}\right) \cdot k \qquad \text{Eq. 14.5}$$

where the bracketed portion is a constant. For potato starch and heavy magnesium oxide compressed at relatively low forces of 0.5 ton and 0.2 ton, respectively, Nogami *et al.* (1966) obtained linear lots of $1/t_D$ *versus* k in conformity with Equation 14.5. For tablets made under low compressional force immersional wetting may, therefore, be the controlling factor for disintegration.

Assuming laminar flow in a capillary and no effect of gravity one may derive Equation 14.6 from Equation 14.2.

$$t = \frac{4\eta L_e{}^2}{D_e \gamma \cos\Theta} \qquad \text{Eq. 14.6}$$

where t is the penetration time, L_e is the length of the capillary, D_e is the pore diameter and the other symbols are as defined above. If the number of layers in a tablet is n, the tortuosity of the capillary in a tablet is taken as 2.5, then the time for water penetration in a tablet may be written as Equation 14.7 from Equation 14.6.

$$t = \frac{4\eta (2.5\, D_A)^2}{D_e \gamma \cos\Theta} \cdot n \qquad \text{Eq 14.7}$$

where D_A is the diameter of the particle of drug in the tablet. If the thickness of the tablet, h, is expressed as $h = D_A \cdot n$ then Equation 14.8 may be obtained from Equation 14.7.

$$t = \frac{25\eta}{\gamma} \times \frac{D_A\, h}{D_e \cdot \cos\Theta} \qquad \text{Eq. 14.8}$$

Here t is the penetration time, η the viscosity of liquid and γ its surface tension, h is thickness of the tablet, D_e is the pore diameter and Θ is the contact angle. After

[1] Peek, R. L. and McLean, D. A.: *Ind. Eng. Chem. Anal. Ed.* 6:85, 1934.
[2] Washburn, E. H.: *Phys. Rev.* 17:273, 1921.

deriving Equation 14.8, Nogami *et al.* (1967) obtained a rough correlation of penetrating time, t, with tablet disintegration time. They concluded that the process of water penetration into the tablet is rate-limiting and determines the rate of disintegration rather than the process of separation of particles.

Equation 14.2 indicates that rapid penetration (large k) is produced by large capillaries (large r value). The effect of compressional force on capillary size and porosity has been studied by several investigators. Nogami *et al.* (1963) measured not only the relationship between capillary diameter and compressional force but also the relationship between disintegration time and capillary diameter for magnesium oxide tablets made from granules, containing 5 percent potato starch as disintegrator and 3 percent starch paste as binder, which were sieved 10/20 mesh before compression. The mean capillary diameter (in microns) decreased from 0.197 to 0.102 to 0.086 to 0.069 for compressional forces of 0.5, 1.0, 1.5 and 2.0 tons/cm^2, respectively. The disintegration time of the tablets increased with decrease in the capillary diameter. Hence one of the main effects of increasing the compressional pressure is to reduce the size of the capillary pores in the tablet. This, in turn, decreases the rate of penetration of liquids into the tablet and increases the disintegration time.

Discussion of Variables Involved in Compressed Tablet Manufacture Which May Affect Disintegration Time

Usually the formulator should aim at making his finished tablets disintegrate as rapidly as possible to ensure rapid onset of action of the drug and full physiological availability in human patients. The following review may aid the formulator in achieving this objective. Many of the factors to be discussed not only lower disintegration time but also speed rate of dissolution of the drug from the granules and aggregates produced by the disintegration process.

Surfactants can be effective in improving tablet disintegration when sprayed in solution onto granules containing starch. Improvement was obtained for tablets of calcium lactate, sodium bicarbonate, tricalcium phosphate, magnesium oxide, magnesium trisilicate, acetylsalicylic acid and ammonium chloride. No improvement was obtained for tablets of sodium salicylate, APC and sulfathiazole. The two most effective of 21 surfactants studied were Aerosol OT and Aerosol MA (Cooper and Brecht, 1957). A wetting agent is a surfactant which, when dissolved in water, lowers the advancing contact angle and aids in displacing an air phase at the surface and replacing it with a liquid phase. The contact angle is the angle formed by the tangent to the liquid droplet and the surface over which it spreads. The contact angle may vary between 0°, signifying complete wetting, or it may approach 180° where wetting is insignificant. Equation 14.2 indicates a surfactant has two effects on penetration rate of liquid. The surfactant lowers surface tension, γ, which tends to decrease k, the coefficient of penetration. However, the surfactant also decreases the contact angle, Θ. Since the cosine of 0° is 1.00 and the cosine of 90° is zero the effect of change in contact angle is very important and may overcome the opposing effect of lowering of γ. For example, the surface tension of human gastric juice varies between 35 and 50 dynes /cm compared with a surface tension of water of 72.8 dynes/cm at 20°C. Hence, if the surfactant used is a good wetting agent the addition of surfactant may be expected to change cos θ to a much greater extent than the change in γ, particularly with hydrophobic drugs. Nogami *et al.* (1963) showed that water penetrated more rapidly into aspirin coated with Aerosol OT-water solution, and 0.02 percent Aerosol OT solution penetrated more rapidly into aspirin than water itself. They hypothesized that the contact angle between aspirin crystal and water was near 90° hence cos θ was nearly zero. With surfactant present the contact angle was greatly decreased, cos θ greatly increased, and this increase overcame the opposing effect of decrease in the surface tension by the surfactant. However, with a solid which wet more readily, magnesium oxide, they found that the penetrating rate of water in a magnesium oxide powder bed was faster (greater k value) than for 0.02 percent and 0.2 percent Aerosol OT in water or for water penetrating magnesium oxide coated with Aerosol OT solution. Surfactants are particularly important in capsule formulations where they will aid wetting of hydrophobic drugs and effect deaggregation of fine particles, particularly micronized drugs.

The effect of the type and amount of disintegrant employed may truly be remarkable in some cases. A comparative study of seven disintegrants compressed at three concentrations (5, 10 and 15 percent in a base of spray-dried lactose using magnesium stearate as lubricant with direct compression) disclosed that most rapid disintegration was achieved with corn starch at 10 and 15 percent regardless of storage temperature (room temperature, 100°F and 120°F) of the finished tablets. Also, the change in disintegration time with age was minimal with cornstarch. Over a six-month period a trend toward decreasing disintegration time was affected by the majority of the disintegrants studied. These results appeared to be contrary to results of wet granulated systems which usually demonstrate increasing disintegration time with aging, (Bergman and Bandelin, 1965). The effect of increasing the percentage of disintegrating agent (starch) on mean open capillary diameter of two types of tablets is shown in Table 14.1.

Table 14.1. Effect of Increasing Concentration of Potato Starch as Disintegrator on Mean Open Capillary Diameter with Aspirin and Magnesium Oxide Tablets[a] (from Nogami *et al.*, 1963)

TYPE OF TABLETS	MEAN OPEN CAPILLARY DIAMETER (μ) FOR INDICATED STARCH CONCENTRATION		
	0 PERCENT	5 PERCENT	10 PERCENT
Aspirin	0.36	0.72	1.14
	0.47	0.96	1.43
Magnesium Oxide	0.07	0.27	0.30
	0.09	0.29	0.32

[a]Compressional force was 0.5 ton/cm^2, direct compression

These results indicate that the disintegrating agent (starch) provides a larger capillary diameter and that the capillary diameter increases with increase in the amount of disintegrating agent employed. The greater the capillary diameter the more rapidly water will penetrate the tablet as indicated by Equation 14.2. Two lots of tolbutamide tablets, both containing 0.5 Gm of drug and both meeting USP tablet specifications, were prepared such that one lot, a commercial production lot, Orinase tablets, was identical in all composition and manfuacturing respects except that these tablets contained twice the amount of Veegum as disintegrant as the other experimental lot. The disintegration times of the two lots were 2 and 7.6 minutes for the commerical and experimental lots, respectively, and the dissolution rates were 3.8 and 103 minutes for the commercial and experimental lots, respectively. In a double-blind crossover study in ten normal human subjects every subject at each sampling time (1½, 3, 5 and 8 hours) had a higher serum tolbutamide level after receiving the commercial lot of tolbutamide than after receiving the experimentally contrived, but USP equivalent formulation. The ratio of the areas under the average serum concentration curves were

$$\frac{\text{area for commercial lot}}{\text{area for experimental lot}} = \frac{47.1}{13.2} = 3.57.$$

Average serum sugar levels were also significantly lower ($P<.001$) at both 1.5 and 3 hours following the commercial lot than following the experimental lot (Varley, 1968). Hence a small change in the disintegrant concentration expressed as a percentage of total tablet weight can markedly affect *in vivo* performance of a tablet. Disintegrant and its concentration often affect rate of dissolution more than disintegration time as evidenced by the tolbutamide results above.

Similarly binder and its concentration may affect rate of dissolution more than disintegration time. Phenobarbital tablets formulated with 1 percent ethylcellulose required 60 minutes to release 98 percent of the drug in acid medium, but the disintegration time of the tablets was only 0.5 minutes in water. Increase in binder concentration decreased rate of dissolution of phenobarbital from tablets (Jacob and Plein, 1968). Using starch paste as binder with magnesium oxide there was a negative correlation ($r = -0.81$) between complete dissolution of the drug as determined by thermal analysis and quantity of starch used as binder (Nakai and Kubo, 1960). Hence, in this case, the larger the quantity of binder used, the more readily the tablets disintegrated into smaller particles and the more rapidly the drug dissolved. Such effects must be studied in carefully controlled studies on each drug.

There should be a critical amount of starch for disintegration depending upon the particle size or specific surface area of the ingredients in a tablet. The smaller the particle size of aspirin, the greater the amount of starch which was required for rapid tablet disintegration (Nogami *et al.*, 1967). Similarly, it was reported that there was a critical starch concentration for lowest tablet disintegration for each granule size used to prepare tolbutamide tablets by a dry granulation method (Commons *et al.*, 1968). These results are summarized in Table 14.2 and are in accord with the theory and results of Nogami *et al.* (1967).

Table 14.2. Average Disintegration Time (Minutes) of Tolbutamide Tablets Made by a Dry Granulation Method (from Commons *et al.* 1968)

STARCH CONCENTRATION (PERCENT)	AVERAGE DISINTEGRATION TIME[a] (MINS) FOR GRANULE SIZE INDICATED			
	16/20	20/40	40/60	60/80
6	>30	>30	—	—
7	2.3	22.3	>30	>30
8	1.1	8.8	28.8	>30
9	0.4	0.3	1.9	2.1
10	—	—	0.7	1.0

[a]Disintegration times were determined by the USP XVI method

The mesh size of the granulation can markedly influence disintegration time as indicated by Table 15.3 taken from Forlano and Chavkin (1960).

Table 14.3. USP Disintegration Rates for Sodium Bicarbonate, Lactose and Magnesium Trisilicate Tablets (from Forlano and Chavkin, 1960)

MESH SIZE	SODIUM BICARBONATE (MINUTES)	LACTOSE (MINUTES)	MAGNESIUM TRISILICATE (HOURS)
8-10	8.5	19.5	0.81
10-12	5.0	12.5	1.40
12-16	8.2	13.0	3.80
16-20	14.5	14.5	6.00
20-30	21.0	16.0	10.50
30-40	26.0	18.0	9.58
40-60	29.0	16.0	0.91
60-80	21.0	11.5	0.61
80-100	14.0	13.5	0.71
100-140	34.0	31.5	0.53
140-200	19.0	10.2	0.40
200 mesh and fines	1[a]	6.0	0.32

[a]These tablets crumbled upon ejection

The effect of granule size on disintegration time and rate of dissolution may be different. For example, Levy *et al.* (1963) showed that rate of dissolution of salicylic acid from tablets, prepared in a Carver hydraulic press, decreased in the order 40/60 mesh granules >20/40 >16/20 mesh granules and attributed the increase to the large available surface area with the smaller granules.

The effect of lubricants on disintegration may be attributed to their usually water repellent nature as well as the fact that they are added just prior to compression so that they physically coat the granules (Bergman and Bandelin, 1965). The purpose of a lubricant is to minimize the frictional forces between the die wall and granulation as the tablet is formed and ejected. The ratio

$$R = \frac{\text{maximum lower punch force}}{\text{maximum upper punch force}}$$

was employed by Strickland *et al.* (1960) to evaluate the effectiveness of a large number of lubricants and other compounds for both a sulfathiazole granulation and a sodium bicarbonate

granulation. Their paper may be consulted for the values of R obtained with the different lubricants. Although magnesium and calcium stearates are excellent lubricants they should be used in as low amounts as is consistent with the required lubricating properties since they definitely increase tablet disintegration time and slow rate of dissolution. This statement holds equally true for hard filled capsule formulas as for tablet formulas.

Compressional force is one of the most important determinants of tablet disintegration time and was first studied in a quantitative manner by T. Higuchi *et al.* (1953). They studied the influence of compressional force employed in tablet manufacture on the apparent density, porosity, hardness, disintegration time and average primary particle size of compressed tablets. The data obtained for the sulfathiazole granulations studied indicated there was a logarithmic relationship between the compressional forces and the apparent density or the porosity of the tablets. A plot of percent porosity *versus* logarithm of compressional force was linear over a wide range of force with negative slope such that the porosity decreased markedly as the force increased. Linear plots were obtained when the logarithm of disintegration time was plotted *versus* compressional force; these plots had a positive slope. Hence the rate of change in disintegration time with respect to compressional force increased very rapidly as the compressional force increased for these granulations and method of preparation of the tablets. An example is shown in Table 14.4.

Table 14.4. Effect of Compressional Force on the Disintegration Time of Sulfathiazole Tablets (from T. Higuchi *et al.* 1953)

FORCE (LB)	DISINTEGRATION TIME SEC.	MEDIAN READING SEC.
	45	
	55	
500	90	50
	35	
	50	
	150	
	145	
1,000	220	150
	125	
	215	
	200	
	255	
1,500	330	285
	285	
	295	
	480	
	525	
2,000	560	560
	655	
	970	
	1,070	
	1,180	
2,500	1,450	1,180
	1,110	
	1,530	
	11,300	
4,000	15,030	15,030
	19,130	

Table 14.5. Compressional Force and Disintegration Times for Aspirin, Phenacetin and Caffeine Tablets Prepared on an Instrumented Rotary Tablet Press (from Knoechel *et al.*, 1967)

FORCE (LBS)	DISINTEGRATION TIME (MINS) W/O DISKS[a]	WITH DISKS[b]
2170	15	4.7
2845	19	13.7
3650	27	20.7
4275	31	23.8
4715	33	24.8
5500	37.7	27.8
6080	42.5	27.2
6735	46.5	33.2
7225	52	32.5
7975	54	33.8

[a]Average time for 2 tablets tested individually.

[b]Average time for 6 tablets tested at same time; fluid was pH 1.3 (HCl-NaCl, μ=0.1) in both cases.

The specific surface areas of compressed tablets, measured by low temperature nitrogen adsorption, undergo marked changes during the compressional process, exhibiting pronounced maxima at 2500 lbs for ⅝-inch tablets (Higuchi *et al.* 1953).

Using an instrumented rotary tablet machine, Knoechel *et al.* (1967) found that disintegration time essentially increased linearly with increase in compressional force in the 2000 to 8000 lbs force range for a previously wet granulated and slugged experimental mixture containing aspirin, phenacetin and caffeine. This type of dependency was obtained in this case when values for tablet hardness and fracture resistance had all increased to plateaus when plotted against compressional force. Representative data is shown in Table 14.5.

Chronological Bibliography on Disintegration for Disintegration of Dosage Forms In Vitro and In Vivo Parts I through V

1. Proctor, B. S.: *Pharm. J. 21*:562, 1862.
2. Toplis, W. G.: *Am. J. Pharm. 87*:518, 1915.
3. Wruble, M. S.: *Am. J. Pharm. 102*:318, 1930.
4. Losinski, E. and Diver, G. R.: A Direct Method for Studying Efficiency of 'Enteric' Tablets, *J. Am. Pharm. Assoc. 22*:143-145, 1933.
5. *Pharmacopoeia Helvetica* V, 1934.
6. Wruble, M. S.: Enteric Coatings I. A Laboratory Method for the Study and Control of Enteric Coatings, *J. Am. Pharm. Assoc. 24*:570-574, 1935.
7. Bukey, F. C. and Bliven, C. W.: Errors in Reported Studies of Enteric Coatings, *J. Am. Pharm. Assoc. 25*:119-122, 1936.
8. Crane, A. W. and Wruble, M. S.: Enteric Coatings; Clinical Investigation, *Am. J. Roentgenol. Radium Therapy 39*:450, 1938.
9. Berry, F. R.: The Preparation of Compressed Tablets I. The Measurement of the Rate of Disintegration of Compressed Tablets, *Quart. J. Pharm. Pharmacol 12*:501-510, 1939.
10. Oser, B. L., Melnick, D. and Hochberg, M.: Physiological Availability of the Vitamins. Study of Methods for Determining Availability in Pharmaceutical Products. *Ind. Eng. Chem. Anal. Ed. 17*:401-411, 1945.
11. Selye, F. L.: Absorption of Enteric-Coated Ammonium Chloride, *Can. Med. Assoc. J. 55*:445-447, 1946.
12. Boger, W. P. and Beatty, J. O.: Procaine Penicillin Administered Orally: Comparison With Sodium Penicillin, *J. Invest. Dermatol. 15*:373-379, 1950.
13. Higuchi, T., Rao, A. N., Busse, L. W. and Swintosky, J. V.: The Physics of Tablet Compression II. The Influence of Degree of Compression on Properties of Tablets, *J. Am. Pharm. Assoc. Sci. Ed. 42*:194-200, 1953.
14. Wright, S. S., Purcell, E. R., Kass, E. H. and Finland, M.: Penicillin G and Benzethacil by Mouth: Comparison of Penicillin Levels in Plasma of Normal Men After Single Oral Doses. *J. Lab. Clin. Med. 42*:417-429, 1953.
15. Schulert, A. R. and Weiner, M.: The Physiological Disposition of Phenylindanedione in Man, *J. Pharmacol. Exptl. Therap. 110*:451-457, 1954.
16. Chapman, D. G., Crisafio, R. and Campbell, J. A.: The Relationship between *in vitro* Disintegration Time of Sugar Coated Tablets and Physiological Availability of Riboflavin, *J. Am. Pharm. Assoc. Sci. Ed. 43*:297-304, 1954.
17. Chapman, D. G., Crisafio, R. and Campbell, J. A.: The Relation Between *in vitro* Disintegration Time of Sugar-Coated Tablets and Physiological Availability of Sodium p-Aminosalicylate, *J. Am. Pharm. Assoc. Sci. Ed. 45*:374- 378, 1956.
18. Endicott, C. J. and Kirchmeyer, F. J.: Relationship Between *in vitro* Tablet Disintegration and Physiological Availability, *Drug Std. 24*:193-199, 1956.
19. Feinblatt, T. M. and Ferguson, E. A.: Timed Disintegration Capsules. An *in vivo* Roentgenographic Study, *New Engl. J. Med. 254*:940, 1956.
20. Wagner, J. G.: The Coating of Tablets, Pills and Capsules, in *Remington's Practice of Pharmacy*, 11th Ed., E. W. Martin and E. F. Cook, Eds., The Mack Publishing Company, Easton, Pa, 1956, pp. 400-419.
21. Cooper, B. F. and Brecht, E. A.: Surfactants in Tablets to Improve Disintegration *J. Am. Pharm. Assoc. Sci. Ed. 46*:520-524, 1957.
22. Tarnowski, C. E.: The Absorption of Shellac-Coated PAS Granules with Special Reference to the Age of the Preparations, *Acta Tuberc. Scand. 34*:76-82, 1957.
23. Juncher, H. and Raaschou, F.: The Solubility of Oral Preparations of Penicillin V, *Antibiotic Med. Clin. Therapy 4*:497-507, 1957.
24. Chapman, D. G., Chatten, L. G. and Campbell, J. A.: Physiological Availability of Drugs in Tablets, *Can. Med. Assoc. J. 76*:102-105, 1957.
25. Wagner, J. G., Veldkamp, W. and Long, S.: Correlation of *in vivo* with *in vitro* Disintegration Times of Enteric Coated Tablets: *J. Am. Pharm. Assoc. Sci. Ed. 47*:681-685, 1958.
26. Gruber, C. M., Jr., Ridolfo, A. S. and Tosick, W. A.: An Enteric Compression Coating II. *In vivo* Studies with Barium Sulfate-Potassium Iodide and Barium Sulfate Tablets, *J. Am. Pharm. Assoc. Sci. Ed. 47*:862-866, 1958.
27. Souder, J. C. and Ellenbogen, W. C.: Laboratory Control of Dextro Amphetamine Sulfate Sustained Release Capsules, *Drug Std. 26*:77-83, 1958.
28. Wagner, J. G., Brignall, T. W. and Long, S.: Enteric Coatings II. Starch (and Amylose) Acetate Phthalates, *J. Am. Pharm. Assoc. Sci. Ed. 48*:244-249, 1959.
29. Morrison, A. B., Chapman, D. G. and Campbell, J. A.: Further Studies on the Relation Between *in vitro* Disintegration Time of Tablets and the Urinary Excretion Rates of Riboflavin, *J. Am. Pharm. Assoc. Sci. Ed. 48*:634-637, 1959.
30. Nogami, H., Hasegawa, J. and Nakai, Y.: Studies on Powdered Preparations II. Studies on Tablet Disintegration of Calcium Carbonate by Thermal Analysis, *Chem. Pharm. Bull. (Tokyo) 7*:331-337, 1959; *ibid.* III. Studies on Disintegration of Basic Magnesium Carbonate Tablet, *ibid. 7*: 337-342, 1959.
31. Mahoney, T.: "The Merchants of Life," Harper & Brothers Publishers, New York, 1959, p. 133.
32. Strickland, W. A., Higuchi, T. and Busse, L. W.: The Physics of Tablet Compression X. Mechanism of Action and Evaluation of Tablet Lubricants, *J. Am. Pharm. Assoc. Sci. Ed. 49*:35-40, 1960.
33. Forlano, A. J. and Chavkin, L.: The Effect of Granule Size Upon Disintegration Time and Capping in Compressed Tablets, *J. Am. Pharm. Assoc. Sci. Ed. 49*:67-69, 1960.
34. Wagner, J. G. and Long, S.: Enteric Coating III. An Improved Enteric Coating and Its *in vitro* Evaluation, *J. Am. Pharm. Assoc. Sci. Ed. 49*:121-127, 1960.
35. Wagner, J. G., Veldkamp, W. and Long, S.: Enteric Coating IV. *In vivo* Testing of Granules and Tablets Coated with Styrene-Maleic Acid Copolymer, *J. Am. Pharm. Assoc. Sci. Ed. 49*:128-132, 1960.
36. Wagner, J. G., Ryan, G. W., Kubiak, E. and Long, S.: Enteric Coatings V. *p*H Dependence and Stability, *J. Am. Pharm. Assoc. Sci. Ed. 49*:133-139, 1960.
37. Wagner, J. G.: A Note on the Correlation of *in vivo* with *in vitro* Disintegration Times of Enteric Coated Tablets, *J. Am. Pharm. Assoc. Sci. Ed. 49*:179, 1960.
38. Morrison, A. B. and Campbell, J. A.: The Relationship Between Physiological Availability of Salicylates and Riboflavin and *in vitro* Disintegration Time of Enteric Coated Tablets, *J. Am. Pharm. Assoc. Sci. Ed. 49*:473-478, 1960.
39. Swintosky, J. V. and Blythe, R. H.: The Excretion of Free Salicylate from an Enteric Coated Tablet and a Compressed Tablet, *Drug Std. 28*:5-8, 1960.
40. Nakai, Y. and Kubo, Y.: Studies on Powdered Preparations IV. Studies on Disintegration of Magnesium Oxide Granules and Tablets by Thermal Analysis, *Chem. Pharm. Bull. (Tokyo) 8*:634-640, 1960.
41. Nakai, Y.: Studies on Powdered Preparations V. Studies on Particle Size Determination and Tablet Disintegration of Acetylsalicylic Acid by Thermal Analysis, *Chem. Pharm. Bull. (Tokyo) 8*:641-646, 1960.
42. Levy, G. and Knox, F. G.: The Biological Activity

of Orally Administered Desiccated Thyroid, *Am. J. Pharm. 133*:255-256, 1961.

43. Engel, L.: "Medicine Makers of Kalamazoo," McGraw-Hill Book Company, Inc., New York, 1961, pp. 22-27.

44. Wagner, J. G.: Biopharmaceutics: Absorption Aspects, *J. Pharm. Sci. 50*:359-387, 1961.

45. Wagner, J. G.: The Coating of Tablets, Pills and Capsules, in *Remington's Practice of Pharmacy*, 12th ed., E. W. Martin and E. F. Cook, eds., The Mack Publishing Company, Easton, Pa., 1961, pp. 476-494.

46. Morrison, A. B., Perusse, C. B. and Campbell, J. A.: Relationship Between *in vitro* Disintegration Time and *in vivo* Release of Vitamins from A Triple-Dose Spaced-Release Preparation, *J. Pharm. Sci. 51*:623-626, 1962.

47. Weiss, A., Pittman, E. R. and Graham, E. C.: Aspirin and Gastric Bleeding, *Am. J. Med. 31*:266-277, 1961.

48. Kaplan, L. L. and Kish, J. A.: Gasket Insert Modification of U.S.P. Tablet Disintegration Apparatus, *J. Pharm. Sci. 706*, 1962

49. Nelson, E.: Physiochemical and Pharmaceutic Properties of Drugs That Influence Results of Clinical Trials, *Clin. Pharmacol. Therap. 3*:673-681, 1962.

50. Schroeter, L. C., Tingstad, J. E., Knoechel, E. L. and Wagner, J. G.: The Specificity of the Relationship Between Rate of Dissolution and Disintegration Time of Compressed Tablets, *J. Pharm. Sci. 51*:865-874, 1962.

51. Ida, T., Takahashi, S., Noda, K., Kishi, S., Nakagami, S. and Utsumi, I.: Protective Coatings XVI. Disintegration of Protective-Coated Tablets as Determined by Urinary Excretion in Humans, *J. Pharm. Sci. 52*:472-474, 1963.

52. Levy, G., Antkowiak, J. M., Procknal, J. A. and White, D. C.: Effect of Certain Tablet Formulation Factors on Dissolution Rate of the Active Ingredient II. Granule Size, Starch Concentration, and Compression Pressure, *J. Pharm. Sci. 52*:1047-1051, 1963.

53. Macek, T. J.: Influence of Product Formulation on Therapeutic Activity, *Minnesota Pharmacist 18*:17-18, 22, 27, 30, 1963.

54. Morrison, A. B. and Campbell, J. A.: Physiological Availability of Drugs in Oral Dosage Forms, *Indian J. Pharm. 25*:209-214, 1963.

55. Nogami, H., Fukuzawa, H. and Nakai, Y.: Studies on Tablet Disintegration I. The Effect of Penetrating Rate on Tablet Disintegration, *Chem. Pharm. Bull. (Tokyo) 11*:1389-1398, 1963.

56. Hecht, G. and Huyck, C. L.: Two Disintegrating Agents *versus* Cornstarch for Compressed Tablets, *J. Pharm. Sci. 23*:112-114, 1964.

57. Middleton, E. J., Davies, J. M. and Morrison, A. B.: Relationship Between Rate of Dissolution, Disintegration Time, and Physiological Availability of Riboflavin in Sugar-Coated Tablets, *J. Pharm. Sci. 53*:1378-1380, 1964.

58. Wagner, J. G.: Biopharmaceutics: Gastrointestinal Absorption Aspects, *Antibiotica and Chemotherapia, Advances 12*:53-84, 1964.

59. Corbas, H. F.: Enteric Coated Thyroid as a Cause of Relapse in Myxedema, *Calif. Med. 100*:364-365, 1964.

60. Levy, G. and Hollister, L. E.: Failure of the U.S.P. Disintegration Test to Assess Physiological Availability of Enteric Coated Tablets, *N. Y. J. Med. 64*:3002-3005, 1964.

61. Brudney, N., Stewart, D. J. and Eustice, B. T.: Rates of Dissolution of Tolbutamide Tablets, *Can. Med. Assoc. J. 90*:980-981, 1964.

62. Lachman, L.: The *in vivo* Effectiveness of Enteric-Film Coatings Applied to Hydrochlorothiazide-Potassium Chloride Tablets by a Programmed Automatic Coating Process, *Current Therap. Res. 6*:491-504, 1964.

63. Morrison, A. B. and Campbell, J. A.: Tablet Disintegration and Physiological Availability of Drugs, *J. Pharm. Sci. 54*:1-8, 1965.

64. Bergman, L. A. and Bandelin, F. J.: Effects of Concentration, Aging and Temperature on Tablet Disintegrants in a Soluble Direct-Compression System, *J. Pharm. Sci. 54*: 445-447, 1965.

65. Steinberg, W. H., Frey, G. H., Masci, J. N. and Hutchins, H. H.: Method for Determining *in vivo* Tablet Disintegration, *J. Pharm. Sci. 54*:747-752, 1965.

66. Leonards, J. L. and Levy, G.: Absorption and Metabolism of Aspirin Administered in Enteric Coated Tablets, *J. Am. Med. Assoc. 193*:99-104, 1965.

67. Strivastava, L. K. and Maney, P. V.: Development and Testing of Enteric Coatings, *Mfg. Chemist 36*:55-58, 1965.

68. Naito, S. I. and Hirai, M.: Studies in Absorption and Excretion of Drugs XV. Inactive Isopropylantipyrine Tablets, *Jap. J. Pharm. Chem. 36*:163-167, 1965.

69. Clark, R. L. and Lasagna, L.: How Reliable are Enteric-Coated Aspirin Preparations?, *Clin. Pharmacol. Therap. 6*:568-574, 1965.

70. Lu, F. C., Rice, W. B. and Mainville, C. W.: A Comparative Study of Some Brands of Tolbutamide Available in Canada Part II. Pharmaceutical Aspects, *Can. Med. Assoc. J. 92*:1166-1169, 1965.

71. Feinstein, W. and Bartilucci, A. J.: Comparative Study of Disintegrating Agents, *J. Pharm. Sci. 55*:332-334, 1966

72. Ingram, J. T. and Lowenthal, W.: Mechanism of Action of Starch as a Tablet Disintegrant I. Factors That Affect the Swelling of Starch Grains at 37°, *J. Pharm. Sci. 55*:614-617, 1966.

73. Patel, N. R. and Hoppenon, R. E.: Mechanism of Action of Starch as a Disintegrating Agent in Aspirin Tablets, *J. Pharm. Sci. 55*:1065-1068, 1966.

74. Merenda, S. J. and Green, D. M.: X-Ray Evaluation of Tablet Disintegration and Gastric Passage, *Pharmacologist 8*:180, 1966, No. 2.

75. Tillis, H. H.: The Microspherule Concept of Enteric Coated Salicylates, *J. Med. Soc. New Jersey 63*:416-417, 1966.

76. Rasmussen, S.: Intestinal Absorption of Quinine from Enteric Coated Tablets, *Acta Pharmacol. Toxicol. 24*:331-345, 1966.

77. Nogami, H., Nagai, T. and Uchida, H.: Studies on Powdered Preparations XIV. Wetting of Powder Bed and Disintegration Time of Tablet, *Chem. Pharm. Bull. (Tokyo) 14*:152-158, 1966.

78. Knoechel, E. L., Sperry, C. C. and Lintner, C. J.: Instrumented Rotary Tablet Machines II. Evaluation and Typical Applications in Pharmaceutical Research, Development, and Production Studies, *J. Pharm. Sci. 56*:116-130, 1967.

79. Schroeter, L. C.: Dissolution Rate *versus* Disintegration Time as an Indication of *in vivo* Drug Availability, *Ann. Pharm. Congr. Industrial Panel,* N.Y., St. John's University, April 25, 1967, p. 17.

80. Nogami, H., Hasegawa, J. and Mujamoto, M.: Studies on Powdered Preparations XX. Disintegration of the Aspirin Tablets Containing Starches as Disintegration Agents, *Chem. Pharm. Bull. (Tokyo) 15*:279-289, 1967.

81. Ingram, J. T. and Lowenthal, W.: Mechanism of Action of Starch as a Tablet Disintegrant II. Effect of Pepsin and Surfactants on Swelling of Starch Grains at 37°, *J. Pharm. Sci. 57*:187-188, 1968.

82. Marks, A. M. and Sciarra, J. J.: Effect of Size on Other Physical Properties of Granules and Their Corresponding Tablets, *J. Pharm. Sci. 57*:497-504, 1968.

83. Jouhan, A. J., Garnett, E. S. and Wallington, J. S.: Postassium Absorption—A Comparison of *in vitro* and *in vivo* Studies, *J. Pharm. Sci. 57*:617-620, 1968.

84. Jacob, J. T. and Plein, E. M.: Factors Affecting Dissolution Rates of Medicaments from Tablets II. Effect of Binder Concentration, Tablet Hardness, and Storage Conditions on the Dissolution Rates of Phenobarbital from Tablets, *J. Pharm. Sci. 57*:802-805, 1968.

85. Commons, K. C., Bergen, A. and Walker, G. C.: Influence of Starch Concentration on the Disintegration Time of Tolbutamide Tablets, *J. Pharm. Sci. 57*:1253-1255, 1968.

86. Varley, A. B.: The Generic Inequivalence of Drugs, *J. Am. Med Assoc. 206*:1745-1748, 1968.

CHAPTER 15

Introduction to Rate of Dissolution in Vitro and in Vivo

Introduction

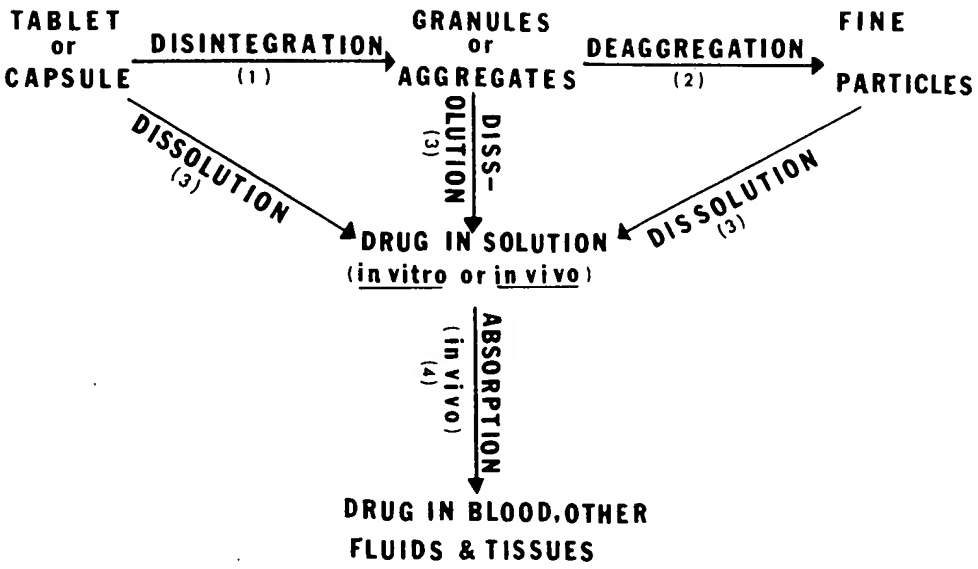
DISSOLUTION IS THE ACT OF DISSOLVING. RATE OF DISSOLU*tion* is the rate of dissolving of a chemical or medicament from the solid state. In biopharmaceutics rate of dissolution usually refers to the rate of dissolving of the medicament from an intact dosage form or from fragments or particles formed from the dosage form during the test. *Rate of solution* and *rate of dissolution* may be used interchangeably as was done by Hixson and Crowell (1931). Although the first article cited* (Noyes and Whitney, 1897) employed *rate of solution* in its title, most current authors appear to prefer *rate of dissolution* or *dissolution rate*.

Scheme 15.1 indicates the processes involved when a tablet or capsule is exposed to fluid under suitable conditions *in vitro* or in the gastrointestinal contents *in vivo* after oral administration. Dissolution of the drug occurs not only from the fine particles of the drug ultimately produced but also to a small degree from the intact dosage form before its disintegration and from the fragments and agglomerates produced after disintegration. Dissolution occurs simultaneously from several types of solid as the scheme indicates. In most *in vitro* test systems nothing analogous to process 4 is included. However in some *in vitro* test systems there is another compartment which, in a sense, simulates "drug in blood, other fluid and tissues." For example, in the dialysis method (Barzilay and Hersey, 1968) a dialyzing membrane is employed. One may also perform simultaneous dissolution and partitioning studies *in vitro* (Niebergall *et al.* 1967) in which case the drug dissolved in an aqueous phase during a test is transferred to an organic solvent immiscible with the aqueous phase. *In vivo*, as the scheme indicates, process 4 involves absorption of the drugs. The drug dissolved in the gastrointestinal contents must diffuse in the aqueous fluids to the gastrointestinal barrier and then be transported through the barrier to the circulation. For most drugs absorption involves adsorption and/or simple partitioning followed by diffusion in the lipoid barrier. In a few cases an active transport process or a different specialized process may be involved.

Dissolution Rate-Limited Absorption

As indicated formerly, there is adequate evidence to conclude that the rate at which a drug dissolves from its

*Citations refer to the chronological bibliography, page 133.



Scheme 15.1

intact or fragmented dosage forms in the human gastrointestinal tract, or in a parenteral injection site, often partially or completely controls the rate at which the drug appears in blood (*i.e.*, the rate of absorption). There is also adequate evidence to conclude that in many cases *in vitro* rate of dissolution test results can be used to *explain* observed differences in results obtained in animals and human subjects or patients. When the dissolution process (process 3 of Scheme 15.1) is very much slower (*e.g.*, less than 1/20 the rate) than the disintegration process (process 1), the deaggregation process (process 2) and the absorption process (process 4) then dissolution essentially completely controls absorption rate. There may be many cases when two or more of the processes proceed at a rate within a factor of 20 of each other in which cases rate of dissolution would only partially control absorption rate. It should be noted, however, that the rates of the processes of disintegration, deaggregation and dissolution are all dependent upon the composition and method of preparation of the dosage form. These rates are all largely dependent upon *pharmaceutical* factors which the formulator can alter. The reasons for measuring disintegration times and rates of dissolution were presented formerly* and should be reviewed at this time.

Historical Highlights

In 1897 Noyes and Whitney published their law which concerns the rate at which solids dissolve in their own

solutions. The law resulted from experiments in which they measured the amount of substance (benzoic acid and lead chloride) dissolved at different times when constant surface cylindrical sticks of the substance were rotated in water. They explained the dissolution process on the assumption that a very thin layer of saturated solution was formed at the surface of the solid and that the rate at which the solid dissolved was governed by the rate of diffusion from this saturated layer into the main body of the solution.

Brunner and Tolloczko (1900, 1901, 1903) showed that the proportionality constant relating the rate of change of concentration to the concentration difference in the Noyes-Whitney equation (1897) depended upon the surface area of the exposed solid, the intensity of agitation or velocity of fluid flowing across the solid, the temperature, the structure of the surface and the experimental apparatus.

Nernst and Brunner (1904) advanced a theoretical generalization of the Noyes-Whitney law to include all kinds of heterogeneous reactions. They postulated that the velocity of a heterogeneous reaction was determined by the velocities of the diffusion processes that accompanied it. This included the concept that the solute-solution equilibrium is set up at the boundary surface practically instantaneously compared with the rate of diffusion. They used Fick's law of diffusion to establish a relationship between the proportionality constant involved and the diffusion coefficient of the solute. In this way they were able to estimate the thickness of the film or diffusion layer at the surface of the solid.

Over the years there have been several critics of the Nernst-Brunner (1904) theory; one of these was Wilderman (1909); Wurster and Taylor (1965) in their review refer to others. However, in general, with some modifications the theory has withstood the test of time.

In 1931 Hixson and Crowell wrote an excellent review of the theory of the dissolution of solids and derived their "cube root law" in which the velocity of solution of a solid in a liquid is expressed as a function of the surface area and the concentration. The derivation of their "cube root law" is based on the following assumptions: (1) dissolution takes place normal to the surface of the dissolving solid; (2) the same effect of agitation is observed on all areas of the surface; (3) no stagnation of the liquid takes place in any region; and (4) the solid particle remains intact through the dissolution process.

In 1932 Klein was the first investigator to determine the rate of dissolution of a compressed tablet. A year later, Elliott (1933), using Klein's apparatus which Elliott called a Solvometer, published plots of amounts of drug dissolved against time following tests on compressed tablets of five different drugs. He attempted "to show the influence exerted upon the rate of solution by two important variables—temperature and surface in contact with the liquid." Elliott's tablets apparently had essentially constant surface areas during dissolution since he found that the rates of solution were essentially constant until about nine-tenths of the tablets was dissolved.

King and Brodie (1937) studied dissolution of rotating cylinders of benzoic acid in water and in sodium hydroxide and potassium hydroxide solutions. They explained their data on the basis of the Nernst-Brunner film theory which assumes linear concentration gradients of all species in the diffusion layer. Later, W. I. Higuchi *et al.* (1958) showed where the assumption of linear concentration gradients would fail.

In 1938 Marshall *et al.* clearly showed the dose dependence of blood levels of sulfanilamide and acetylsulfanilamide in dogs. They stated, "Acetyl-sulfanilamide is much less soluble in water than sulfanilamide and might be expected to be absorbed less readily and completely than sulfanilamide." They showed that increasing the dose of sulfanilamide from 0.16 Gm/Kg to 1.6 Gm/Kg caused an approximate tenfold increase in peak blood level of sulfanilamide; however, increasing the dose of the less soluble acetylsulfanilamide from 0.16 Gm/Kg to 1.6 Gm/Kg caused very little increase in the peak blood level. The concept of a relatively fixed time for drug at the absorption sites and relative rates of dissolution (which in turn are related to the solubilities) readily explain such data.

Oser, Melnick and Hochberg (1945) employed urinary excretion data in proposing the concept of physiological availability of the vitamins from pharmaceutical products. They demonstrated clearly that within certain limits a direct relationship exists in normal subjects between the urinary excretion of water-soluble vitamins and the amount ingested. This relationship provided a means to assess physiological availability of the vitamins in pharmaceutical products by measurement of urinary excretion of the vitamins in man after ingestion of products intended for oral administration. Such data have been used in biopharmaceutics to correlate with *in vitro* data such as disintegration time and rate of dissolution.

In 1951 Danckwerts introduced another model for dissolution where one imagines macroscopic packets of solvent reaching the solid-liquid interface by eddy diffusion in some random fashion. During its residence at the interface the packet is able to absorb solute according to the usual laws of diffusion. These surface elements are continuously replaced by new packets of solvent. This surface renewal process may then be related to the solute transport rate.

In the same year, Edwards (1951) predicted that "for aspirin in tablet form the rate controlling process, as far as analgetic action in the blood is concerned, is the dissolution within the stomach and intestine." This prediction was based on the *in vitro* rate of dissolution of aspirin as a function of *p*H, the rate of diffusion of aspirin in aqueous solutions, and theoretical calculations. However, he did not test his hypothesis *in vivo* nor did he seem to be aware of the earlier work of Marshall *et al.* (1938) and Oser *et al.* (1945).

In 1953 Smith, Kline and French Laboratories marketed the first "sustained-release" Spansule product. Subsequently, a host of prolonged action and sustained-release products have been marketed. The results achieved

*See Chapter 10, page 64.

with these products are directly related to slower absorption of the contained drugs relative to conventional dosage forms. Indirectly, the slower absorption is attributable to slower dissolution of the drug from the dosage forms in the gastrointestinal tract of man.

Nelson (1957) showed there were marked differences in the intrinsic *in vitro* rates of dissolution of theophylline salts and hypothesized that these differences could explain differences in peak blood levels and prolongation of blood levels observed by other workers when these salts were administered orally to human subjects. Nelson stated, "Other factors remaining constant, solution rate determines blood level and rate of build-up of blood level with time."

In the same year, Brodie and Hogben (1957) ascribed the long duration of action of the centrally acting muscle relaxant, zoxazolamine, to precipitation of the drug in the intestines where, due to its low solubility, it dissolves slowly and is absorbed slowly during many hours after oral administration.

In 1958 W. I. Higuchi and associates examined the problem of dissolution rates of solids in reactive solutions by the simultaneous chemical reaction and diffusion (SCRD) method. This was an experimental and theoretical study of the influence of bases and buffers on rates of dissolution of acidic solids. The SCRD method employed the Nernst-Brunner model and assumed nonlinear concentrative gradients in a single diffusion layer. They showed that complex rate equation which they derived could be reduced to more simple equations under certain conditions which may be readily determined by a consideration of the dissociation constants of the acids and bases involved in a particular system.

Nelson (1959) and Nelson and Schaldemose (1959) discussed solution rate-limited and non-solution rate-limited absorption and pointed out the value of urinary excretion kinetics for evaluation of rate of drug absorption.

Shenoy, Chapman and Campbell (1959) published data on the urinary excretion rates and physiological availability measured in man, and *in vitro* rates of release from eight different pelleted products of amphetamine labeled as being of the sustained-release type. Only two of the eight preparations tested demonstrated constant urinary excretion at an adequate level and were quantitatively available. They stated, "The data suggest that marked diferences may be expected in the clinical effect of 'sustained-release' products presently on the market."

Simultaneously, in the same journal, Wiegand and Taylor (1959) and Wagner (1959) published papers indicating that many sets of percent released-time data, previously published and based on *in vitro* tests of prolonged action and sustained release preparations, could be adequately described by apparent first order kinetics.

In 1960, Levy and Hayes discussed the physicochemical basis of the buffered acetylsalicylic acid controversy. They concluded that the incidence of local irritation and the absorption rate of acetylsalicylic acid is a function of its dissolution rate in its particular dosage form. They described a dissolution assembly, later to become known as the "beaker method," which provided mild agitation conditions for determination of dissolution rates of tablets.

Wagner, Carpenter and Collins (1960) compared plasma 17-OHCS levels in the dog following oral administration of compressed tablets and *p*H-dependent coated granules containing prednisolone. They also compared plasma 17-OHCS levels in man following oral administration of compressed tablets, *p*H-dependent coated granules and *p*H-independent coated granules containing prednisolone in man. *In vitro* release rates as a function of *p*H were also presented. These data clearly show one must be very careful about extrapolating *in vitro* data to man. Although the *p*H-dependent and *p*H-independent granules released drug entirely different *in vitro*, the plasma 17-OHCS levels measured over a 24-hour period following administration to man were essentially equivalent. Both granules forms provided prolonged plasma 17-OHCS levels compared with those achieved with the tablet.

Stone (1960) filed a patent to cover a method of solubilizing relatively insoluble antibiotics. The method involved dissolving the antibiotic and a highly soluble polymeric material such as polyvinylpyrrolidone (and other specified polymers) in a mutual essentially nonaqueous solvent and then removing substantially all the solvent to obtain a readily soluble residue. Later, Simonelli, Mehta and Higuchi (1968) showed that drugs so treated with PVP were essentially amorphous in nature and this accounted for the high dissolution rates of the drugs so treated.

In 1961 Levy correlated dissolution and absorption rates of different commercial aspirin tablets and proved that Edwards' (1951) hypothesis was correct.

The review entitled "Biopharmaceutics: Absorption Aspects" (Wagner, 1961) established biopharmaceutics as a new subject. This review clearly established the role of dissolution rate studies in this new field.

In the same year, at a Teachers' Seminar in Pharmacy, T. Higuchi (1961) discussed the role of crystal structure on availability and stability of some pharmaceuticals. This led to much subsequent research on use of different polymorphic forms and solvates to improve dissolution characteristics of drugs.

In the same year, Sekiguchi and Obi (1961) developed a new technique to achieve particle size reduction of a drug and thereby permit sparingly soluble drugs to become dispersed finely in the fluids of the gastrointestinal tract. The method involves the formation of a eutectic mixture of the drug (solid at room temperature) and a pharmaceutically inert, readily soluble carrier. Sulfathiazole in a eutectic mixture with urea exhibited higher absorption and urinary excretion in man than ordinary sulfathiazole after oral administration. Later, Sekiguchi *et al.* (1964) studied the chloramphenicol-urea system. Still later, Goldberg, Gibaldi and Kanig (1965) summarized literature on eutectic mixtures and solid solutions and studied the acetaminophen-urea system (1966), the griseofulvin-succinic acid system (1966) and the chloramphenicol-urea system (1966).

In 1962, Hamlin, Nelson, Ballard and Wagner showed that increasing the intensity of agitation in dissolution

rate studies on two polymorphic forms of methylprednisolone resulted in a loss of sensitivity and a failure to distinguish between the polymorphs with respect to dissolution rate. This study emphasized the need for low intensities of agitation in many *in vitro* dissolution rate tests. Levy and Procknall (1964) studied the same polymorphs by the rotating disk method and confirmed that the observations of Hamlin *et al.* (1962) were due to the intrinsic properties of the drugs and not to the particular apparatus employed. They stated, "It is certainly appropriate to characterize the dissolution rate dependence of drugs on agitation intensity aspect of their biopharmaceutical evaluation." The observations of Hamlin *et al.* (1962) were explained on the basis of the Danckwerts' model by Goyan (1965) and on the basis of a double barrier model by Wurster and Taylor (1965). However, the most plausible explanation of the observation's of Hamlin *et al.* (1962) was given by W. I. Higuchi *et al.* (1967).

Schroeter, Tingstad, Knoechel and Wagner (1962) reported that with some tablets there was a quantitative relationship between rate of dissolution (as reflected by the $t_{50\%}$ values) and disintegration time but with other tablets there was no such relationship. Where a quantitative relationship existed, the slopes of the lines relating the variables varied widely and depended upon the particular drug involved and, in one case, upon the presence and absence of sodium chloride as an ingredient in the tablets. These authors questioned the use of plastic disks in the official tablet disintegration test. They also reevaluated the data of Chapman *et al.* (1956) and showed that physiological availability of p-aminosalicylate was correlated with dissolution rate as well as with disintegration time.

Levich (1962) showed that the hydrodynamics associated with the rotating disks method for determination of rates of dissolution are such that the diffusion layer model *per se* is not applicable and that the so-called "Levique equation" must be used to interpret data obtained by this method.

Schroeter and Wagner (1962) described the first automated dissolution rate apparatus. A modification of this apparatus was reported later by Schroeter and Hamlin (1963). Other automated apparatus for dissolution rate studies were described by Niebergall and Goyan (1963), Pernarowski *et al.* (1968), McClintock *et al.* (1968) and Barzilay and Hersey (1968).

W. I. Higuchi and Hiestand (1963) derived an equation to describe the dissolution rate of a particle with time in a diffusion-controlled process then applied the equation to a hypothetical powder whose particles are approximately log-normally distributed. For relatively large particles the change in volume with change in radius is small and may be disregarded; but for very small particles the change in volume with change in radius is large and must be taken into consideration. W. I. Higuchi, Rowe and Hiestand (1963) applied the equation to the dissolution rate of micronized methylprednisolone in aqueous solutions and reasonably good agreement between experiment and theory was obtained.

Shefter and T. Higuchi (1963) showed that the anhydrous and organic solvate forms of several drugs dissolved more rapidly than the corresponding hydrated forms. They derived equations relating the solubility products and diffusional constants to rates of solution of organic solvates. They pointed out that the formation of organic solvates of many highly insoluble drugs is a very useful method for effecting rapid dissolution of such drugs.

T. Higuchi (1963) derived equations which gave theoretically expected rates of release of solid drugs incorporated into solid matrices based on several model systems.

W. I. Higuchi, Nelson and Wagner (1964) demonstrated that within the framework of the diffusion layer model the total solubility method based on the Noyes-Whitney law (1897) and the SCRD method (W. I. Higuchi *et al.*, 1958) give the same results when all of the diffusion coefficients may be set equal to the same value. Because diffusion coefficients of solute molecules do not differ much in general and other uncertainties—such as variation of dissociation constants and solubilities with ionic strength and other solute interaction effects—are frequently overriding factors, it would be expected that the total solubility method should explain most experimental results as well as the SCRD method.

Goyan (1965) used Danckwerts' (1951) penetration model to derive equations for the dissolution of solids in a multiparticulate system. The equations obtained are capable of explaining the deviation from linearity of Hixson and Crowell (1931) type cube root plots.

W. I. Higuchi, Mir and Desai (1965) developed theory for the dissolution rate of polyphase mixtures based on the diffusion layer model. The theory explained the observation of Nelson (1958) that there was a maximum in the plot of dissolution rate *versus* composition for the benzoic acid-trisodium phosphate system. In the opinion of the writer the use of basic compounds with poorly soluble weakly organic acidic drugs is not utilized in tablets and capsules to nearly the extent that it should be. This article of W. I. Higuchi *et al.* (1965) clearly outlines the theory for such use.

Hamlin, Northam and Wagner (1965), using compressed pellets in a standard apparatus, showed that the initial rate of dissolution (sink conditions) was directly proportional to the solubility of the drug in the dissolution medium, in conformity with the Noyes-Whitney (1897) law for a large number of drugs of widely varying structures. This supported the conclusion of W. I. Higuchi, Nelson and Wagner (1964). Exceptions to such a relationship are self-coating pellets such as described by Levy and Procknall (1962) and Higuchi and Hamlin (1963).

Levy, Leonards and Procknall (1965) developed a method of correlating absorption data estimated from urinary excretion of salicylate following oral adminstration of aspirin to man with *in vitro* rate of dissolution data derived from the same dosage forms of aspirin.

In a series of important papers W. I. Higuchi and associates (Desai, Simonelli and Higuchi, 1965; Desai,

Singh, Simonelli and Higuchi, 1966; Singh, Desai, Simonelli and Higuchi, 1968; Schwartz, Simonelli and Higuchi, 1968) elucidated the role of a number of factors controlling the rate of drug release from a variety of plastic and wax matrices and developed and applied theoretical approaches to this area.

Knoechel, Sperry and Lintner (1967), using an instrumented rotary tablet process which they designed and instrumented, obtained much experimental data on the relationship between rate of dissolution and compressional force and other variables when compressed tablets are made under actual production conditions.

W. I. Higuchi, Bernardo and Mehta (1967) reported a correlation between the rates of reversion of the metastable forms to the stable forms during dissolution and the crystal growth rates of the stable form for two polymorphic forms of both sulfathiazole and methylprednisolone. The usefulness of a polymorphic form of a drug to increase rate of dissolution may be gauged not only from this paper but from the previous one of W. I. Higuchi, Lau, T. Higuchi and Shell (1963) and the papers of Wurster and Taylor (1965).

Niebergall, Patil and Sugita (1967) presented an *in vitro* method for the simultaneous determination of dissolution rate and partitioning into a water-immiscible solvent in contact with the dissolution medium. The kinetics of the system were found to be in agreement with expectations for diffusion controlled processes.

Finholt and Solvang (1968) compared the kinetics of *in vitro* dissolution of phenacetin and phenobarbital in powdered form in human gastric juice with those in dilute hydrochloric acid containing varying amounts of polysorbate 80. The effect of polysorbate 80 on the rate of dissolution of phenacetin was shown to be due only to a small extent to its solubilizing power; but the principal effect of the surfactant was to decrease the interfacial tension between the drug particles and the dissolution medium. They showed that the surface tension of the dissolution medium has an appreciable effect on the dissolution kinetics of the two drugs studied.

Aguiar *et al.* (1968) demonstrated that deaggregation of powder in capsules after disintegration of the capsule shell may be a most important factor in drug availability and rate of dissolution. Such deaggregation kinetics may explain, in large part, the marked differences in physiological availability of various brands of chloramphenicol capsules reported by Glazko *et al.* (1968).

Thomas and Armstead (1968) showed that under static conditions rate of dissolution was proportional to the 4/3rd power of solubility when the lower faces of large potassium chloride crystals dissolved in mixtures of ethanol and water. They illustrated a regular pattern of etch pits on the crystal faces due to convective stirring action.

Brice and Hammer (1969) measured oxytetracycline serum concentration in 16 two-way crossover studies in 20 subjects each study. A single lot of Pfizer oxytetracycline capsules was the control treatment in each of the studies. Sixteen lots of oxytetracycline from 13 different suppliers constituted the other treatments. In each study the Pfizer oxytetracycline capsules produced superior serum levels. Seven of the 16 lots from other suppliers produced serum levels which were generally below the usually accepted minimum therapeutic level of 0.6 μg/ml. In an attempt to explain the differences these authors performed various disintegration and dissolution tests. They found that, in general, lots which gave poor serum levels also had slower rates of dissolution *in vitro*. They stated, "However, it is apparent that predictions of therapeutic availability cannot be made with precision from *in vitro* experiments in this case."

Tingstad and Riegelman (1969) described a continuous flow apparatus for determination of rates of dissolution. Rather than the usual cumulative plot of percent dissolved *versus* time, this type of test produces a plot of instantaneous rate of dissolution *versus* time.

Wagner (1969) discussed the interpretation of percent dissolved-time data derived from conventional testing of tablets and capsules from which drug dissolves reasonably rapidly. It was shown why, when surface area decreases exponentially with time, after some lag time, one would expect the data to obey first order kinetics. A distribution function, such as the logarithmic-normal distribution or the logistic-logarithmic distribution, may better be utilized to linearize percent dissolved-time data.

Blythe (1969) discussed a systematic approach to bioavailability testing. He pointed out that in future years a great deal of effort will have to be expended to obtain the human data and the *in vitro* data necessary to solve the generic equivalence-inequivalence problem.

Many other papers of historical, research and student interest have, by necessity, been omitted from this summary of the history of rate of dissolution *in vitro* and *in vivo*. However, it is hoped that this summary will orient the reader to the literature on rate of dissolution and make the subsequent material to be presented more meaningful in terms of historical perspective.

CHAPTER 16

Measurement and Interpretation of in Vitro Rates of Dissolution

Introduction

INTRINSIC RATES OF DISSOLUTION ARE DETERMINED ON pure or essentially pure compounds, usually under sink conditions (*i.e.*, dissolution medium less than about 10 percent saturated with the compound during the test), in a standardized test procedure where the geometry of the system is fixed and held constant and using a constant surface area disk or pellet. Usually, under such conditions, a plot of amount of compound dissolved *versus* time is linear on cartesian coordinate graph paper and the slope of the line is equal to the rate of dissolution in units of weight per unit time. Since the exposed surface area is known the intrinsic rate of dissolution may be expressed as weight dissolved per unit surface area per unit time (*e.g.*, mg/cm²/hr). Intrinsic rates of dissolution are a complex function of surface geometry when various shaped pellets are suspended in a turbulent flow field (Rippie and Johnson, 1969*). When the lower faces of large crystals dissolve in a solvent under static conditions a regular pattern of etch pits on the crystals are observed due to convective stirring action (Thomas and Armstead, 1968). Most methods which have been used have obviated these difficulties by utilizing only one surface of a flat-faced disk prepared by compressing the pure compound in a die at high pressure, and using appropriate agitation conditions.

Theory of Intrinsic Rates of Dissolution

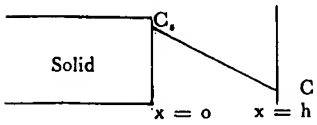
Noyes and Whitney (1897) rotated cylinders of benzoic acid and lead chloride in water then analyzed the solution at various intervals of time. The surface area of the cylinders remained essentially constant during their studies. They derived the Noyes-Whitney law which may be stated as:

$$\frac{dC}{dt} = k(C_s - C) \qquad \text{Eq. 16.1}$$

where C is the concentration of solute at time t, dC/dt is the rate of change of concentration with respect to time, k is a constant with dimension of 1/time, and C_s is the concentration of a saturated solution of the solute in the dissolution medium.

*Citations refer to the chronological bibliography in chapter 20, page 133.

Nernst and Brunner (1904) were the first to discuss the diffusion layer model of a polycrystalline solid dissolving in pure solvent. Their model is shown schematically in Scheme 16.1. In this model it is assumed that there is a liquid layer ("film") of



Scheme 16.1

thickness, h, in which there is a neglible velocity component in the x-direction (perpendicular to the surface). At $x>h$, it is assumed that rapid mixing is present and no concentration gradients exist in this region. At $x = 0$ (the solid-liquid interface) it is assumed that solid-solution equilibrium exists. Then the rate of solute movement and therefore the dissolution rate are determined entirely by Brownian motion diffusion of the molecules in the liquid diffusion layer ($0<x<h$). If a one component, one phase solid of macroscopic ($\gtrsim$1mm) dimensions of low to moderate ($\approx$ 5%) solubility dissolves without disintegration and without chemical reaction into a solvent *under mild to high agitation conditions*, then the dissolution rate according to this model will be given by:

$$\frac{dW}{dt} = \frac{DS}{h}(C_s - C) \qquad \text{Eq. 16.2}$$

where W is the mass of solute dissolved at time t, dW/dt is the rate of dissolution (mass/time), D is the solute molecule diffusion coefficient, h as defined in Scheme 16.1 is the effective diffusion layer ("film") thickness and C_s and C are defined above. In the context of the above the intrinsic rate of dissolution of the solute would be $1/S \cdot dW/dt$ which we may call G.

If V is the volume of the dissolution medium, then

$$W = V \cdot C \qquad \text{Eq. 16.3}$$

Substitution of Equation 16.3 into Equation 16.2 and rearrangement gives Equation 16.4.

$$\frac{dC}{dt} = \frac{DS}{Vh}(C_s - C) \qquad \text{Eq. 16.4}$$

Comparison of Equation 16.4 with Equation 16.1 yields

$$k = \frac{DS}{Vh} \qquad \text{Eq. 16.5}$$

Table 16.1. Dimensions of Variables, Constants and Groups in Dissolution Rate Equations

VARIABLE, CONSTANT OR GROUP	DIMENSIONS
W	weight or mass
D	length^2/time or area/time
h	length
S	length^2 or area
C or C_s	weight/length^3 or weight/volume
dW/dt	weight/time
G or $1/S \cdot dW/dt$	weight/(area x time)
D/h	length/time
DS/h	volume/time
D/Vh	$\frac{1}{\text{length}^2 \text{ x time}}$ or $\frac{1}{\text{area x time}}$
k or DS/Vh	1/time

In writing such equations different ways it is important to keep in mind the dimensions of the variables, constants and groups. Table 16.1 is an aid in keeping the dimensions clarified.

Under sink conditions (*i.e.*, C very small compared with C_s) Equation 16.2 may be written as Equation 16.6 if we substitute G for $1/S \cdot dW/dt$.

$$G = \frac{D\,C_s}{h} \qquad \text{Eq. 16.6}$$

Under carefully controlled experimental conditions D, C_s and h will all be constants hence the intrinsic rate of dissolution, G, will be a constant.

If we write the reduced form of Equation 16.2 for sink conditions as

$$\frac{dW}{dt} = \frac{DSC_s}{h} \qquad \text{Eq. 16.7}$$

and integrate Equation 16.7 we obtain

$$W = \frac{DSC_s t}{h} \qquad \text{Eq. 16.8}$$

whence,

$$\frac{W}{S} = \left(\frac{DC_s}{h}\right) \cdot t = G \cdot t \qquad \text{Eq. 16.9}$$

Hence a plot of the amount dissolved, W, divided by the constant surface area, S, against time, t, will yield the intrinsic rate of dissolution, G.

Under static conditions a different equation is applicable. C. Wagner (1949) gave Equation 16.10 to describe the average rate of dissolution per unit surface area from a rectangular surface suspended vertically in dissolution media under static conditions.

$$R'_n = 0.726\, D\, C_s \left(\frac{g}{HD\eta} \cdot \frac{\Delta\rho}{\rho_o}\right)^{1/4} \qquad \text{Eq. 16.10}$$

where R'_n is the mean rate of dissolution per unit surface area, H is the height of the rectangular plate, η is the viscosity of the diffusion layer, $\Delta\rho$ is the difference in density between the diffusion layer and the bulk solution, g is the gravitational constant, ρ_o is the density of the dissolution medium and D and C_s are defined above. Equation 16.10 was verified by determining weight loss of thin plates of rock salt suspended vertically in unstirred water on a spring balance by means of a silver wire. It was concluded that under such conditions diffusion and natural convection due to the density difference between a saturated solution and pure water are the rate-determining factors.

Nelson (1958 a) first described his *hanging pellet method* and applied the method to determination of rates of dissolution of both the free acids and sodium salts of benzoic acid, phenobarbital, salicylic acid, succinic acid and sulfathiazole in 0.1 N hydrochloric acid, 0.1 M phosphate buffer and 0.1 M borate buffer. The method consisted of attaching a compressed flat-faced disk of the compound to a microscope slide or small stainless steel plate by means of wax or paraffin then coating the edge of the pellet with wax or paraffin so that only the upper circular face of the disk was exposed. The whole assembly was then suspended in the dissolution medium which was maintained under static conditions. Levy (1963) claimed that the hanging pellet method of Nelson "has the disadvantage of variable 'agitation' since differences in concentration of drugs in the boundary layer and the resulting differences in specific gravity and rate of flow over the surface of the solid tend to accentuate dissolution rate differences between drugs."

Rotating Disk Method

In this method a flat-faced disk of the compound is inserted into a holder which in turn is affixed to the end of a stirring shaft. A constant speed motor drives the shaft and turns the pellet in the fluid at a known angular velocity. Levich (1962), assuming laminar flow and a diffusion-controlled process, derived the so-called *Levich equation* below for the rotating disk.

$$J = 0.62\, D^{2/3}\, \nu^{-1/6}\, \omega^{1/2}\, C_s \qquad \text{Eq. 16.11}$$

where J is the rate of dissolution, D is the diffusion coefficient, ν is the kinematic viscosity, ω is the angular rotation and C_s is the solubility of the compound in the dissolution medium. Hence, in a diffusion-controlled process J is a linear function of $\omega^{1/2}$. In deriving this equation Levich used an infinite series approximation to an integral but ignored higher order terms. Gregory and Riddiford (1956) reevaluated the integral involved and using higher order terms derived the equation below.

$$J = 1.61 \left(\frac{D}{\nu}\right)^{1/3} \sqrt{\frac{\nu}{\omega}} \left[1 + 0.35 \left(\frac{D}{\nu}\right)^{0.36}\right] C_s \qquad \text{Eq. 16.12}$$

where the symbols have the same meanings as described above under Equation 16.11.

Levy and Tanski (1964) described an apparatus for determination of intrinsic rates of dissolution by the rotating disk method. It affords precision speed control, wide range of rotation rates, good shaft concentricity and maintains constant speed over extended periods of time. The equipment was built from a model T-8 Sigmamotor pump, a model 14 Revco Zero Max Speed changer with a vernier control and the speedometer cable from a truck.

The rotating disk method has been used by several authors to study intrinsic rates of dissolution of several drugs in a variety of media including acetylsalicylic acid and aluminum acetylsalicylate in 0.1 N hydrochloric acid and in alkaline media (Levy and Sahli, 1962), acetylsalicylic acid and salicylic acid (Levy, 1963) methylprednisolone polymorphs I and II in water (Levy and Procknall, 1964), various sulfonamides (Nogami *et al.*, 1966), and benzoic acid in water and solutions of polyoxyethylene (23) lauryl ether (Gibaldi *et al.*, 1968). Commenting on the report of Gibaldi *et al.* (1968), Simonelli *et al.* (1968) stated: "The hydrodynamics associated with a rotating disk is such that the diffusion layer model *per se* is not applicable and the Levich

equation [or the equations of Gregory and Riddiford (1956) and Cooper and Kingery (1962)] must be used. The rotating disk model represents one of the few instances of an exact mathematical solution to a classical hydrodynamic problem, while the diffusion layer model assumes a uniform one-dimensional diffusion layer. Therefore, the diffusion layer model cannot be applied to the diffusional flux from a rotating disk, which is influenced by both a centrifugal force and a concentration gradient."

Miscellaneous Methods with Stirring

Nelson (1957) mounted compressed flat-faced disks of various compounds on microscope slides so that only one face was exposed. The slide containing the disk was then placed at the bottom of a beaker containing stirred solvent. Parrott *et al.* (1958) employed compressed pellets with a stirred fluid contained in a flask. Hamlin *et al.* (1965) used compressed flat-faced disks held in a polyethylene holder which was inserted 6.3 cm in a 4 fl. oz. oval bottle containing 120 ml of dissolution medium at 37°; the capped bottle was fastened by a spring clip to the periphery of a wheel submerged in a water bath held at 37°. At least four pellets of each compound were rotated at a constant speed for different intervals of time selected so that concentration of solute was always less than 10 percent of the solubility value. The pellets were removed, dried and the dimensions measured. The average of the initial and final surface areas was used to estimate the rate. The solutions were assayed by ultraviolet spectrophotometry. When such methods as these are employed then Equations 16.2 through 16.9 are usually applicable.

Methods of Measuring Rates of Dissolution of Powders and Fine Particle Drugs

A wide variety of dissolution rate apparatus employing different types of agitation have been used to study the dissolution of powdered drugs or drugs in the form of fine particles. The earliest references are those of Brunner and Tolloczko (1900, 1901, 1903, 1907), Nernst and Brunner (1904) and Wilderman (1909). Lewis (1916) applied diffusion layer theory to the extraction of a solid by a liquid for two cases: (1) that in which the solid carrier is a porous material and holds the solute in solution in its pores, and (2) that in which the solute is held in a gel such as salt in skins. Hixson and Crowell (1931) carried out research with the purposes of generally investigating the subject of agitation and establishing a basis which might serve for a quantitative comparison of different agitations. They derived their well-known "cube root law" in the manner shown below.

Derivation of Cube Root Law

(a). The General Case. Let W_o be the weight of the crystal at the start ($t = 0$) and W be the weight of the crystal at time t. Let W_s be the weight of solid needed to saturate the liquid under given conditions of temperature, volume, etc., S be the surface area of the crystal at time t, V be the volume of the solution and d be the density of the crystal. Then dW/dt will be the rate of dissolution or rate of change of weight of the crystal. Using the Noyes-Whitney Equation 16.1 we may write:

$$\frac{dW}{dt} = -K_2 S (C_s - C) \qquad \text{Eq. 16.13}$$

where K_2 is a positive constant with dimensions of length /time, S is a variable and C_s and C are defined under Equation 16.1.

Now $W_o - W$ is the weight of the crystal that has dissolved up to time t, and $(W_o - W)/V = C$, if $C = 0$ when $t = 0$. Similarly $W_s/V = C_s$. Substituting these in Equation 16.13 gives

$$V(dW/dt) = -K_2 S (W_s - W_o + W) \qquad \text{Eq. 16.14}$$

Provided there is no change in the shape of the crystal as it dissolves, its surface area varies as the two-thirds power of its volume, owing to that property of similar geometrical solids, or $S \alpha v^{2/3}$, or since $W/d = v$, then $S = k_s W^{2/3}$, where k_s may be considered as containing the density and a shape constant whose value would depend upon the shape of the crystal.

Substituting for S in Equation 16.14 and setting $W_s - W_o = g$, we obtain the following equation where K_1 is a combined constant (*i.e.* $K_1 = k_s K_2$)

$$V (dW/dt) = -K_1 W^{2/3} (g + W) \qquad \text{Eq. 16.15}$$

Rearrangement of Equation 16.15 and integration yields

$$V \int \frac{dW}{gW^{2/3} + W^{5/3}} = -K_1 \int dt + C' \qquad \text{Eq. 16.16}$$

where C′ is a constant of integration.

After letting $g^{1/3} = a$, $W_o^{1/3} = b$, and $W^{1/3} = x$, and knowing that when $t = 0$, $W = W_o$ and $C = 0$, we obtain the equation for the general case where the initial weight taken is either greater or less than, but not equal to, the amount needed for saturation (*i.e.*, $W_o = W_s$).

$$K_1 t = \frac{V}{a^2} \left[\sqrt{3} \tan^{-1} \frac{2\sqrt{3}\, a\, (b - x)}{3a^2 + (2b - a)(2x - a)} + 1.1513 \log \frac{(a + b)^2 (a^2 - ax + x^2)}{(a + x)^2 (a^2 - ab + b^2)} \right] \qquad \text{Eq. 16.17}$$

It may be seen in Equation 16.17 that there is a relation between t and the cube root of the weight at that time, $W^{1/3}$, which has for simplicity been written as x. All other values are constants or are known values of W. If certain conditions are invoked by imposing certain experimental restrictions Equation 16.17 may be simplified greatly.

(b.) Special case No. 1. Let the initial weight of crystals taken be equal to the amount necessary for saturation, *i.e.*, $W_s = W_o$, or $g = a = 0$.
Substitution into Equation 16.15 we obtain:

$$V(dW/dt) = -K_1 W^{5/3} \qquad \text{Eq. 16.18}$$

which integrates to give

$$K_2 t = V(W^{-2/3} - W_o^{-2/3}) \qquad \text{Eq. 16.19}$$

In Equation 16.19, $K_3 = \frac{2}{3} K_1$ or writing with the same symbols as in Equation 16.17 to show the relationship to the general case,

$$K_3 t = V\left(\frac{1}{x^2} - \frac{1}{b^2}\right) \qquad \text{Eq. 16.20}$$

Special Case No.2. In this case the concentration gradient, $(C_s - C)$, is maintained essentially constant by keeping the dissolution medium sufficiently dilute. Equation 16.13 then becomes Equation 16.21.

$$\frac{dW}{dt} = -K_3 W^{1/3} \qquad \text{Eq. 16.21}$$

Equation 16.21 integrates to

$$K_4 t = W_0^{1/3} - W^{1/3} \qquad \text{Eq. 16.22}$$

where $K_4 = \frac{2}{3} K_3$. The usefulness of Equation 16.22 has been shown by Parrott *et al.* (1955) and Niebergall and Goyan (1963 a and b).

(d) Discussion. The cube root law was developed for one particle or crystal but its extension to a number of particles is valid. The change to the use of n particles involves the substitution of $n^{2/3}$ times the cube root of the sum of the n individual weights for the sum of the cube roots of each of the individual weights takes singly, or the substitution of

$$n^{2/3}(w_1 + w_2 + w_3 + \ldots\ldots + w_n)^{1/3}$$

for the expression

$$(w_1^{1/3} + w_2^{1/3} + w_3^{1/3} + \ldots\ldots + w_n^{1/3}$$

This is justified even when the value of n is small, provided the variation between the particles is small. In such cases $n^{2/3}$ appears as part of the constant.

The assumptions involved in the derivation of the cube root law are as follows:

(1) The process of dissolution takes place normal to the surface and the effect of agitation of the liquid against all parts of the surface is essentially the same.

(2) The crystal shape is predominantly spheroidal throughout its solution process.

(3) It is not necessary to postulate any definite geometrical shape for the particle undergoing dissolution and no other measurements beyond weight are necessary.

(4) Differences in rates of dissolution from different crystal faces are neglible since all faces participate to give an average or mean rate.

(5) Agitation in the neighborhood of the particle is so intense that there is no sensible stagnation of the liquid in that region resulting in a slow rate of diffusion being set up. The law does not apply where there is no agitation.

Dissolution of Crystals Freely Falling in a Rising Solvent

Crystals of sodium chloride or potassium chloride (0.3 to 2.4 Gm) falling freely in a rising solvent so that the crystals remained steadily in the middle of the vessel were studied by Zdanovski (1946). Cubical crystals in this arrangement approximately maintained their cubical shape. If the mass of crystals decreased from w_0 to w_1 within t minutes, C_s is the concentration of a saturated solution, C is the concentration of the following liquid, and d is the density of the crystals, then

$$k = \frac{d^{2/3}(w_0^{1/3} - w_1^{1/3})}{2\,t\,(C_s - C)} \qquad \text{Eq. 16.23}$$

The relationship between the constant k and the absolute temperature of the medium was given by:

$$\log k = A - \frac{B}{T} \qquad \text{Eq. 16.24}$$

where T is the absolute temperature and A and B are constants.

Danckwerts' Model

In this model one imagines macroscopic packets of solvent reaching the solid-liquid interface by eddy diffusion in some random fashion. During its residence at the interface the packet is able to absorb solute according to the laws of diffusion. These surface elements are continuously replaced by new packets of solvent. The surface removal process may then be related to the solute transport rate. Danckwerts (1951) elaborated the model for dissolution of a gas in a liquid. Johnson and Huang (1956) demonstrated the applicability of the model for dissolution from a flat surface into turbulent liquid after studying five systems, namely benzoic acid-water, salicylic acid-water, salicylic acid-benzene, succinic acid-n-butanol and succinic acid-acetone.

Under the conditions outlined in the text above Equation 16.2 the Danckwerts' model leads to Equation 16.25.

$$G = p^{\frac{1}{2}} D^{\frac{1}{2}} (C_s - C) \qquad \text{Eq. 16.25}$$

where G is the rate of dissolution per unit surface area, p is the mean rate of production of fresh surface and D, C_s and C have the same meanings as defined above under Equation 16.1 and 16.2. Goyan (1965) used the Danckwerts' penetration model to derive an equation for the dissolution of solids in a multiparticulate system. Equation 16.26 was shown to hold for multiparticulate systems at high stirring rates where formerly Niebergall *et al.* (1963 b) had provided evidence that the Hixson-Crowell cube root law did not hold.

$$G = \left[D/r + p^{\frac{1}{2}} D^{\frac{1}{2}}\right] C_A \qquad \text{Eq. 16.26}$$

In Equation 16.26 r is the radius of the spherical particle, C_A is the steady state concentration and the other symbols have the meanings given above.

For a monodisperse multiparticulate system Goyan (1965) derived Equations 16.27 and 16.28.

$$-\frac{dW}{dt} = S\left[D/r + D^{1/2}\,p^{1/2}\right]C_A \qquad \text{Eq. 16.27}$$

which integrates to

$$W_o^{1/3} - W^{1/3} = \left[\frac{2e + b\,(W^{1/3} + W_o^{1/3})}{3\,(W^{1/3} + W_o^{1/3})}\right]t \qquad \text{Eq. 16.28}$$

where W is the weight at time t and S is the surface area of N particles, $e = \dfrac{D\alpha N^{2/3} C_A}{\gamma}$, $b = D^{1/2}\,p^{1/2}C_A$ $\alpha N^{1/3}$, t is the time and γ and α are constants containing density and geometric terms.

Dissolution of Micronized Powders

For large particles (>ca 10μ) the change in volume with change in radius, $\Delta v/\Delta r$, is very small and may be disregarded. However, for small particles (<ca 10μ), $\Delta v/\Delta r$ is quite large and must not be neglected. Particle size distribution effects may be taken into account by selecting a particle size distribution function that is time-dependent and combining it with the appropriate dissolution rate equation. For the general case of a micronized powder with a distribution of particle sizes W. I. Higuchi and Hiestand (1963) derived Equation 16.29.

$$Q = \frac{\int_{a_o t}^{al_o} \left(a_o^2 - \left(\frac{2D\Delta Ct}{\rho}\right)^{3/2} n(a_o)\,da_o}{\int_{aS_o}^{al_o} a_o^3\, n\,(a_o)\,da_o} \qquad \text{Eq. 16.29}$$

In Equation 16.29 Q is the fraction of powder not dissolved at time t, al_o is the radius of the largest particle at zero time, as_o is the radius of the smallest particle at time zero, a_o is the radius of a particle at time zero, D is the diffusion coefficient, $\Delta C = C_s - C$, ρ is the density and n is the number of particles of a given size.

Subsequently, W. I. Higuchi *et al.* (1963) showed that the distribution of particle size of micronized methylprednisolone could be approximated by the function

$$n\,(a_o) = K/a_o^2 \qquad \text{Eq. 16.30}$$

For al_o and as_o the value of 0.5μ and 9.0μ, respectively, were chosen to provide the fit. These limits corresponded to a size range of 1 to 18μ diameter. Substituting Equation 16.30 into Equation 16.29 gave Equation 16.31.

$$Q = \frac{\int_{a_o t}^{al_o} \frac{1}{a_o^2}\left(a_o^2 - \frac{2D\Delta Ct}{\rho}\right)^{3/2} da_o}{\int_{as_o}^{al_o} a_o\, da_n} \qquad \text{Eq. 16.31}$$

Appropriate integration of Equation 16.31 gave Equation 16.32.

$$Q = \frac{2}{al_o^2 - as_o^2}\left[\left(\frac{al_o}{2} + \frac{2D\Delta Ct}{\rho\, al_o}\right) al_o^2 - \frac{2D\Delta Ct}{\rho}\right)^{1/2} + \frac{3D\Delta Ct}{\rho} \ln\left\{\frac{\left(\frac{2D\Delta Ct}{\rho}\right)^{1/2}}{al_o + \left(al_o^2 - \frac{2D\Delta Ct}{\rho}\right)^{1/2}}\right\}\right] \qquad \text{Eq. 16.32}$$

Theoretical curves plotted from Equation 16.32 agreed quite well with experimental data obtained for dissolution of the micronized methylprednisolone in water when the suspensions were placed in bottles attached to a wheel and rotated at 6 r.p.m. while the temperature was maintained at 25° C.

Dissolution of Powdered Drug Attached to Pressure-Sensitive Tape

Goldberg *et al.* (1965) fastened pressure sensitive tape to a frame made by bending a No. 2 paper clip into a rectangle with a short handle. The tape presented a taut adhesive surface onto which a pre-weighed quantity of drug particles was uniformly dusted as a monoparticulate layer. A 600 ml beaker was modified to contain two stainless steel runners attached to its inner wall by means of epoxy cement. The runners were placed just far enough apart to serve as tracks for the tape frame so that the frame and tape could be rapidly introduced into the dissolution vessel. A constant speed motor attached to a laboratory jack allowed the motor to be raised and lowered and to position the stirrer paddle in the dissolution medium. Dissolution of 50/60 mesh (250-300μ) benzoic acid and salicylamide from the tape was observed in 400 ml of water maintained at 37°. Data were shown to confirm to the Hixson-Crowell cube root law as extended by Niebergall and Goyan (1963) for a system of N equal-sized particles.

Dissolution-Rate Measurement with a Coulter Counter

Edmendon and Lees (1965) followed the change in particle size of hydrocortisone acetate in suspensions by means of a Coulter Counter. The dissolution rate was expressed as diamenter loss per unit time in conformity with Equation 16.33.

$$d_t = d_o - k_2\,t \qquad \text{Eq. 16.33}$$

Here d_t is the diameter at time t, d_o is the initial diameter and k_2 is a constant. They found that the dissolution rate of hydrocortisone acetate under their experimental conditions was in conformity with Equation 16.33 with k_2 equal to 1.68μ/hr. equivalent to 108 μg/cm² surface area/hr.

CHAPTER 17

Measurement of in Vitro Rates of Dissolution from Capsules and Tablets

Requirements for Test Procedure

DISSOLUTION RATE APPARATUS SUITABLE FOR BOTH RESEARCH and quality control purposes should meet certain criteria. The most important of these are as follows. First, the apparatus should be economically practical. Ideally, the apparatus should be capable of being fashioned from standard laboratory equipment. Apparatus, such as the Brinkman Desago Resomat, which costs $1,165.00, would be undesirable just from the point of view of high cost per unit. Secondly, the apparatus should be scientifically realistic. It is essential that the inherent variability in the apparatus be less than the inherent variability in the products being tested. This requires that the essential components be rigidly definable and reproducible. The apparatus must be capable of reproducing a given intensity of agitation with fixed geometry for successive runs when the settings are maintained constant. There must be the capability of reproducing this result from one copy of the apparatus to the next. Thirdly, the apparatus must be flexible in effective degree of agitation. That is, one must be able to alter the effective degree of agitation by altering stirring rate or some similar parameter.

Types of Apparatus

1. *The U.S.P.-N.F. Tablet Disintegration Apparatus*

Many investigators have utilized this apparatus to determine rate of dissolution during the same test that disintegration time is determined. The apparatus has only one oscillation speed, hence fails to meet the third criterion stated above. Primary agitation intensity is produced by the turbulence of fluid flowing through the basket chamber. The effective degree of agitation is relatively high, but is difficult to define. Measured rates of dissolution are quite rapid for moderately quickly-releasing tablets. Because of the relatively high intensity of agitation some poorly available products have been found to release drug rapidly in the apparatus and results from good and bad products do not correlate well with *in vivo* results. In such cases lower intensities of agitation allowed distinction between the products. Although much early work was performed with the apparatus it was decided by most researchers in 1969 that the apparatus was undesirable for future investigations. This apparatus in modified form, was first introduced by Gershberg and Stoll (1946).*

*For references with an asterisk see end of this article. For those citations not having an asterisk see the Chronological Bibliography of Rate of Dissolution in Vitro and in Vivo on page 133.

2. *Rotational Apparatus—NF XII, Second Supplement*

The apparatus[**] consists of a horizontal rotating shaft to which are attached clamps to hold round screw-capped bottles. The clamps are designed so that the long axis of the bottle is at a right angle to the axis of the shaft, and they are adjusted so that the distance between the axis is about 47.5 mm. The rotating shaft with the attached bottle is mounted in a constant temperature bath, the shaft is connected by a chain drive to an electric motor equipped with a speed-regulating device capable of altering the rotational speed from 6 r.p.m. to 50 r.p.m. This apparatus was introduced into the official compendium to be used in determining rate of release of drugs from timed-release (variously known as delayed-action, extended release, prolonged-action, sustained-action, sustained-release and repeat-action) tablets and capsules. For details of use of this apparatus the official compendium should be consulted. Usually the product is exposed to 60 ml aliquots of fluids of increasing *p*H, successively; for example, *p*H 1.2 (0-1 hour), *p*H 2.5 (1-2 hours), *p*H 4.5 (2-3½ hours), *p*H 7.0 (3½-5 hours) and *p*H 7.5 (5-7 hours). The *p*H 1.2 fluid is Simulated Gastric Fluid T. S. The *p*H 7.5 fluid is Simulated Intestinal Fluid T. S. The other fluids are obtained by mixing the two fluids in certain proportions.

In practice, to obtain constant results, the geometry of the bottles and their positioning relative to the axis of rotation need very rigid definition. For a given speed of rotation, the relative intensity of agitation will depend upon the "rate of fall" of the particles in the fluids. The "rate of fall" is related to the apparent density of the particles and hence dependent upon formulation variables. This apparatus was first introduced by Souder and Ellenbogen (1958).

[**]Available from E. O. Menold Sheet Metal Company, Fifth and Powhatan Avenues, Lester, Penn. 19113.

3. *Rotating-Basket Assembly NF XIII*

This consists of a rotating-basket assembly, preferably fabricated from type 316 stainless steel, a suitable vessel (preferably a 1000 ml resin flask) to contain the dissolution medium, a four-hole cover for the vessel, and a high-torque stirring motor equipped with a speed-regulating device capable of rotation at specified speeds, ±5 percent, varying from 25 r.p.m. to 200 r.p.m. The assembly is immersed in a constant temperature bath maintained at 37±0.5°. The rotating basket is a cylinder 3.6 cm in height and 2.5 cm in diameter, the sides and bottom of which are 40 mesh stainless steel cloth. The cylinder is joined at the seams by welding and is welded at the top and bottom to stainless steel rings. A 6 mm x 30 cm stainless steel rod, attached to a 2.5 cm. plate and three spring clips, is used to hold the basket. The stirring rod of the rotating basket assembly is placed through the center hole of the vessel cover and is centered by suitable means to permit smooth rotation and to prevent wobbling. A thermometer is placed in the second hole of the vessel, and the remaining two holes are used for sampling. The basket is immersed to a point 2.0±0.2 cm from the bottom of the flask. Initially 900 ml of dissolution fluid is placed in the flask and the volume is maintained by adding a volume of dissolution fluid equivalent to that removed for sampling purposes.

At the time of writing the *National Formulary* had provided only preliminary information on this apparatus. The slowest speed suggested was 100 r.p.m. (The U.S.P.-N.F. Tablet Disintegration Apparatus is equivalent to about 200 r.p.m.). From research carried out by several investigators it would appear that a rotation speed of 50 r.p.m. would be more realistic but may present problems with homogeneity of the bath fluid. A major objection to this apparatus appears to be clogging of the wire of the basket by fragments of some dosage forms. If this is common, it could be a serious defect of the apparatus. This apparatus is a

modification of the apparatus suggested by Pernarowski *et al.* (1968).

4. *Beaker Method of Levy and Hayes (1960)*

The assembly consists of a 400 ml Pyrex Griffin beaker containing 250 ml of dissolution fluid which is agitated by a three-blade, 5 cm diameter, polyethylene stirrer attached to an electronically-controlled stirring motor. Stirring rates of 30-60 r.p.m. are usually used. This is sufficient speed to obtain a homogeneous solution for sampling purpose yet low enough not to break down the "microenvironment" of the dosage form being tested. In using the apparatus the stirrer is immersed in the dissolution medium to a depth of 27 mm. and is accurately centered by means of a guide. The beaker is immersed in a constant temperature bath maintained at 37±0.1°. Samples are taken by means of a fritted glass immersion tube of medium porosity and 30 mm diameter.

Results from this method have been correlated with *in vivo* data. The latter consisted of absorption half-times estimated from serum salicylate concentrations by the method of Wagner and Nelson (1963) following oral ingestion of aspirin in several forms. The range of individual subject half absorption times (0.7 to 1.9 hours) fell in the range of the *in vitro* dissolution half-times obtained by using agitation intensities of from 30 to 60 r.p.m. (0.6 to 2.3 hours). The mean absorption half-time (1.3 hours) was equivalent to the *in vitro* dissolution half-time obtained by using a rotational speed of 50 r.p.m. in this procedure (Levy and Hollister, 1965).

Publication of the report (Levy and Hayes, 1960) was a significant advance in dissolution rate methodology. It clearly indicated that for tablets and other solid oral dosage forms low intensities of agitation are highly desirable and more likely to allow distinguishing formulations and products and correlating results with *in vivo* data.

5. *Flask and Stirrer Method of Poole (1969)*

The dissolution vessel is either a 1- or 2-liter three-necked round-bottom flask which allows from 500 to 2000 ml of dissolution medium to be used in the test procedure. The stirring paddle is a 7.6 cm diameter Teflon paddle[••] and is positioned 2.5 cm from the bottom of the flask and centered. The stirring shaft[•••] is 14½ inches long. The stirring rate is maintained at 50 r.p.m. by means of an electronically controlled stirrer. The dissolution vessel is immersed in a constant temperature bath maintained at 37°. The dosage form is introduced through one opening of the three-necked flask. Tablets fall down the wall of the flask and position themselves at the bottom of the round-bottom flask directly under the centered stirring paddle. In the case of capsules a wire spiral around the capsule causes the capsule to sink in the fluid and position itself like the tablets. The solution is pumped from the dissolution vessel through Tygon tubing to a spectrophotometer by means of a peristaltic pump. An intermittent filtration-sampling method, similar in many respects to that described by Schroeter and Hamlin (1963), is used.

The author has used this type of dissolution assembly with silicone rubber tubing[••] and directly pumped the solution through a flow cell using a Sigmamotor peristaltic pump. By use of 0.1, 1.0, 5.0 and 10 cm path length flow cells one may adjust absorbance readings in the ultraviolet region of the spectrum for many drugs to be in the optimum range. With a suitable recorder one may then obtain a continuous plot of amount of drug dissolved *versus* time. Using 1000 ml of dissolution fluid and a rotational speed of 50 r.p.m., a good correlation of *in vitro* results with absorption rates of one drug in man was obtained recently.

6. *Oscillation Equipment of Macdonald et al. (1969)*[•]

The equipment consists of a V-shaped, transparent plastic cylindrical chamber which oscillates freely about its center. A frequency of 25 oscillations per minute was used in studying various tetracycline capsule formulations. In addition to the cylinder, the test assembly consists of a filtering device, polyethylene and latex tubing, a peristaltic pump, a 0.2 cm flow cell and a Beckman DB spectrophotometer equipped with a logarithmic potentiometric recorder. When tablets were tested in this apparatus they usually remained at the bottom of the oscillating chamber in a reasonably fixed position. Capsules, however, usually float on the surface of the test fluid until the gelation dissolves then the capsule contents sinks in the fluid. $T_{80\%}$ values obtained in this apparatus for four different commercially-available tetracycline hydrochloride capsules were rank-order correlated with both the areas under the serum concentration curves over 0 to 6 hours and the amount of tetracycline hydrochloride activity excreted in the urine in the 0 to 8 hours period post-administration.

7. *Flow Through Assemblies with Cumulating Reservoirs*

In these assemblies the dosage form is held in a small vertical glass column through which the dissolution medium flows upward. The solution formed is passed to a reservoir of the fluid and from there the fluid is pumped again to the bottom of the column. Hence there is a constant circulation of fluid from the reservoir through the pump to the bottom of the column containing the dosage form then back out of the top of the column to the reservoir again. The concentration of drug in the dissolution medium in the reservoir increases with increase in time in a similar manner to

[••]Teflon stirring blade, size B, 3″ length, catalog number S-76637, E. H. Sargent and Co.
[•••]Stirring shaft, size A, 14½″ length, catalog number S-76636, E. H. Sargent and Co.

[••]Tubing, silicone, white, opaque, ⅜″ i. d., ½″ o. d., catalog no. RS91-125, F. B. Wright Co., 9999 Mercier St., Dearborn, Mich. 48121.

that in the six methods discussed above. However, the principle differences are that in these flow through assemblies the dosage form or fragments therefrom are exposed to only a small portion of the dissolution medium at any given time, and the dosage form or fragments are not present with the bulk of the dissolution fluid as in the six methods discussed above.

The first such apparatus was probably that of Dr. Wiley of the Food and Drug Administration as reported by Meyers (1960).* This apparatus consisted of a stoppered cylindrical tube with a glass wool filter above the bottom outlet and a side-arm outlet for return of fluid to the reservoir. A pump was used to circulate the fluid at a definite rate from the reservoir through the tube. The apparatus was immersed in a water bath at 37°. Tablets were placed on the filter and were separated from each other by layers of glass wool. Drug was eluted with 100 ml aliquots of circulating fluid.

A modification of this apparatus was recently reported by Baum and Walker (1969).* In this assembly the vertical column is 16 cm long with a 1.8 cm internal diameter. The dosage form is trapped between two 100-mesh stainless steel screens in the upper 7 cm portion of the column. The reservoir is a 25 ml or 500 ml wide-mouth conical flask. The stopper of the flask is fitted with three glass tubes—one connecting to the top of the column, the second connecting to the pump, and the third for taking samples from the fluid in the reservoir. The other side of the pump has a return tube connection to the bottom of the column. The dissolution column and reservoir are partially immersed in a constant temperature bath held at 37±0.1°. When making a test the dissolution medium is poured into the reservoir and allowed to equilibrate with the water bath. The pump is primed by allowing dissolution fluid to flow at a high rate through the pump into the lower part of the dissolution column but not above the lower screen. This procedure expels air from the pump and tubing. The tablet is dropped into the column where it rests on the lower screen. The upper screen is inserted, and above it, the top of the column is stoppered. The pump is started and the flow rate usually held at 70±2 ml/min. Aliquots of solution are removed at specified time intervals from the fluid in the reservoir and assayed for the drug. An equal volume of dissolution fluid is added following each withdrawal to replace the fluid withdrawn. In performing tests with tablets the authors reported that for the most part tablets remain on the bottom screen, but depending on density, trapped air, etc., may rise and rub against the upper screen, thus influencing dissolution.

Data resulting from dissolution tests in such assemblies are cumulative amounts dissolved against time as in the six methods discussed above.

8. *Flow Through Assemblies without Cumulating Reservoir*

These assemblies have similar components to those discussed under number 7 above. The difference is that the reservoir is used only to hold fresh dissolution medium; as the fluid leaves the top of the column after being exposed to the dosage form the solution is collected for assay and not returned to the reservoir. Hence the dosage form and fragments therefrom are continuously exposed to fresh dissolution medium and essentially sink conditions are maintained at all times providing the rate of flow of fluid is fast enough through the column.

Most work on such an assembly seems to have been done by Langenbucher (1969).* In the assembly he described dissolution fluid leaves a reservoir, passes through a metering pump then through a heat exchanger for temperature control then into the column where it flows upwards and out the top of the column. The eluate leaving column is analyzed for drug content, either continuously, or the solution is collected over fixed time intervals—for example 3, 5, 7.5, 10, 15 . . . minutes.

In these assemblies the following parameters determine the dissolution kinetics: volumetric flow rate, Q (cm^3/min.); cross-sectional column area, A (cm^2); and initial drug amount, M_0 (Gm). Since the drug amount is given by the dosage form itself, there remain only two apparatus parameters which are best described as mass-specific quantities: liquid velocity, $Q_A = Q/A$ (cm/min.) and drug amount per unit cell area, $M_{A,0} = M_0/A$ (Gm/cm^2). These two quantities determine the degree of agitation in the liquid as well as the elimination of the dissolved drug from the system. One particular feature of interest is that different drug amounts are dissolved under identical conditions whenever the parameter Q_A and $M_{A,0}$ are equal. This means that the dissolution of N tablets, studied simultaneously in a column with cross-section N • A and with a volumetric flow rate of N • Q is the same as the average of N runs of a single tablet in a cell with cross section A and volumetric flow rate Q—providing one assumes that the tablets are homogeneous.

A similar apparatus to that of Langenbucher (1969)* was described by Tingstad and Riegelman (1969).

These assemblies are distinctly different from the other seven types discussed above. In the previous types data obtained are cumulative amounts dissolved against time. Unless samples are taken at very frequent intervals it is difficult and inaccurate to calculate rates of dissolution from the cumulative amount data. However, with continuous analysis or collection of effluent from the column over short time intervals and subsequent analysis of the aliquots with the flow through assembly without cumulating reservoir the dissolution rate (mass/time) against time is obtained directly. One can also sum the amounts or calculate the areas under the rate curve to different times (equivalent to amounts) to produce the usual plot of cumulative amounts dissolved *versus* time.

9. *Canadian Food and Drug Directorate Apparatus*

This method uses a screen cell located in one upper

corner of the glass jar as the sample holder. Very strong agitation is used to stir the bulk fluid.

10. *Dialysis Methods*

An apparatus described by Ferrari and Khoury (1968) involved the use of a baffled rotating round bottom flask to provide a 'sloshing' action believed by the author to be similar to the agitation received by a tablet in the stomach. The filtered contents of the flask were continuously circulated through a dialyzer. The dialysate was continuously analyzed in a spectrophotometer while the stream is returned to the dissolution flask.

Another dialysis apparatus was described by Marlowe and Shangraw (1967). A plastic dialysis cell had four thicknesses of a thin paper membrane separating the two chambers. Two tablets and 15 ml of dissolution fluid were placed in one compartment and 15 ml of dissolution fluid in the other compartment. The cell was closed and rotated in a water bath, held at 37°, at 15 r.p.m. One ml samples were removed at intervals from the side which initially had only dissolution medium in it.

An automated dialysis method was described by Barzilay and Hersey (1968).

In dialysis methods the data collected are a resultant of not only the disintegration, deaggregation and dissolution processes but also of membrane transport. Introduction of the dialyzing membrane into dissolution rate apparatus seems to the author to needlessly complicate an already complicated situation.

11. *Other Methods*

Unfortunately there appear to be as many different types of dissolution rate apparatus and variations of established apparatus as there are investigators studying dissolution phenomena. Several types of apparatus and variants of apparatus were reviewed by Hersey (1969)* and Baum and Walker (1969).*

Conclusions and Comments

The author believes we will never be able to simulate one individual's intestinal tract, let alone devise an apparatus which will simulate the "average" person's intestinal tract. The physiological situation is extremely complex. For example, bacteria may affect gastrointestinal function more than we think, which in turn may be affected by antibiotics. Hence the author believes that investigations leading to attempts to simulate the gastrointestinal tract by dissolution rate apparatus will be misguided and lead to little if any improvement in obtaining data which will correlate with *in vivo* results.

The author also believes that the concept of a universal dissolution rate test, in the compendium sense, is desirable but largely impractical. Each drug and the dosage forms prepared from it have to be studied individually and usually retrospectively (after *in vivo* data are available) to determine satisfactory and definitive quality control dissolution rate procedures. Dissolution rate specifications should be established only when *in vivo* and *in vitro* data have been correlated. If dissolution rate data have been correlated with *in vivo* data obtained in man then the setting of dissolution rate specifications and inclusion in an official compendium may be desirable. However, one must be very cautious. The USP and NF do not specify the pharmaceutical adjuvant in a monograph on a tablet or capsule of a given drug. An *in vitro-in vivo* correlation established with say four different manufacturers' tablets of a given drug may not apply to a fifth product containing the same drug. This is feasible since a change in pharmaceutical adjuvants can alter the relationships already established.

The dissolution test conditions (apparatus, intensity of agitation and composition of dissolution medium) must be established for all drug products of a given drug in which one has an interest. Sufficient correlation with *in vivo* data must then be performed to establish definitive quality control specifications. Then and only then does one feel confident that the specifications are meaningful. The author believes that future research in dissolution rate should be directed mainly toward establishing correlations of the *in vitro* data with *in vivo* data obtained in man. He also believes that the flask and stirrer method of Poole (1969)* and the flow through type assembly without cumulating reservoir (Langenbucher, 1969)* offer the most promise for the future.

References

1. Gershberg, S. and Stoll, F. D.: Apparatus for Tablet Disintegration and for Shaking-Out Extractions, *J. Am. Pharm. Assoc. Sci. Ed. 35*:284-287, 1946.

2. Poole, J. W.: Some Experiences in the Evaluation of Formulation Variables in Drug Availability, *Drug Inform. Bull. 3*:8-16, 1969.

3. Macdonald, H., Pisano, R., Burger, J., Dornbush, A. and Pelcak, E.: Physiological Availability of Various Tetracyclines, *Drug Inform. Bull. 3*:76-81, 1969.

4. Myers, E. L.: Experimental Determination of Sustained Action, *Drug Cosmetic Ind. 87*:622-711, 1960.

5. Baum, D. C. and Walker, G. C.: Apparatus for Determining the Rate of Drug Release from Solid Dosage Forms, *J. Pharm. Sci. 58*:611-616, 1969.

6. Langenbucher, F.: *In Vitro* Assessment of Dissolution Kinetics: Description and Evaluation of a Column-Type Method, *J. Pharm. Sci. 58*:1265-1272, 1969.

7. Hersey, J. A.: Methods Available for the Determination of *in Vitro* Dissolution Rate, *Mfg. Chemist Aerosol News 40*: 32-35, 1969.

CHAPTER 18

Factors Affecting Rate of Dissolution and Interpretation of Dissolution Rate Data from in Vitro Testing of Tablets and Capsules

Factors Affecting Rate of Dissolution of Drugs from Capsules and Tablets in Vitro and in Vivo

MOST OF THESE FACTORS ARE THE SAME AS THOSE which affect disintegration time of tablets and capsules. Hence at this time these factors should be reviewed in the earlier section.* In the scheme below most of the important factors are summarized.

I. Environmental factors during dissolution

1. Intensity of agitation, rate and type of flow of fluids and geometrical factors.
2. Concentration gradient, *i.e.*, the difference in concentration between the solubility of the drug in the dissolution medium and the average concentration in the bulk fluid.
3. Composition of the dissolution medium. The pH, ionic strength, viscosity, surface tension, etc., are all important and are determined by the composition of the medium.
4. Temperature of dissolution medium.

II. Factors related to the physico-chemical properties of the drug.

A. Factors affecting solubility

1. Polymorphism
2. Amorphous state and solvation
3. Free acid, free base or salt form
4. Complexation, solid solutions and eutectics
5. Particle size
6. Surfactants

*See page 89.

B. Factors affecting surface area available for dissolution

1. Particle size
2. Manufacturing variables

III. Factors Related to the composition and method of manufacture

A. Tablets

1. Amount and type of diluent or filler and other adjuvants such as neutral salts
2. Type of tablet manufacture employed
3. Granule size and size distribution
4. Amount and type of disintegrant and method of incorporating it
6. Amount and type of surfactant (if any) and method of incorporating it
7. Compressional force and speed of compression.

B. Capsules

1. Amount and type of diluent or filler and other adjuvants such as neutral salts
2. Method used to reduce bulk (*e.g.*, granulating or slugging)
3. Granule or powder size and size distribution
4. Amount and type of lubricant and method of incorporating it
5. Amount and type of surfacant (if any) and method of incorporating it
6. The "pressure" applied during filling
7. Composition and properties of the capsule shell

IV. Environmental factors involved with dosage forms

1. Humidity during manufacture
2. Storage conditions for dosage forms
3. Age of dosage forms

Interdependency of Factors

Many of the above factors are interdependent making the situation in a given case often quite complicated. Examples will be given of a few such interdependencies.

If the drug is an alkali metal salt of a weak organic acid (enol, phenol or carboxylic acid), then exposure to hydrochloric acid in the stomach, or to say 0.1 N hydrochloric acid *in vitro*, will cause conversion of some, but not necessarily all, of the drug in the dosage form to the free acid form. Usually, the dissolution rate of this acid form formed in the very acidic fluid and, later when it is exposed to less acidic or basic fluids, will be considerably less than the rate of dissolution of the original salt form in the same fluids. Conversely, if the drug is a free base form then exposure to hydrochloric acid in the stomach or *in vitro* will cause conversion of some, but not necessarily all, of the drug in the dosage form to the salt form. Usually, the rate of dissolution of such a drug in strongly acidic media would be more rapid than it would be if the dissolution medium were less acidic or basic.

Such effects may be important. For example, conversion of a weak acid salt to the corresponding weak acid on the surface of a tablet or the contents of a capsule can form a film which is insoluble in the acidic media, and which prevents penetration of water into the rest of the dosage form thus inhibiting disintegration of a tablet or deaggregation of the powder in a capsule. Hence, even when a dosage form or its fragments reach lower acidic medium in the intestine, or the *p*H is raised in the *in vitro* test, the drug dissolves much more slowly than if the dosage form had been designed to break up very rapidly in strongly acidic media. If the alkali metal salt of a weak acid (*e.g.*, sodium or calcium alginate) were used as an adjuvant in a tablet or capsule precipitation of the corresponding weak acid (alginic acid) would have a similar effect. Specific examples of such effects are as follows. Using the rotating disk method and 0.1 M Tris buffer, *p*H 8.0, and sink conditions, Levy and Procknall (1962)* found that the rate of dissolution of aluminum acetylsalicylate decreased progressively with increase in time due to formation of a basic, water-insoluble aluminum compound on the surface of the pellet. Addition of 1 percent EDTA to the dissolution medium prevented the film formation by chelation of the Al^{3+} ions. Morozowich *et al.* (1962) reported on the release of benzphetamine from pellets of benzphetamine pamoate in 0.12 N hydrochloric acid and proposed that the rate of dissolution was controlled by a layer of pamoic acid which was deposited on the surface of the pellet. Later, W. I. Higuchi and Hamlin (1963) examined the model for the general case of release of an amine in acid solution from a pellet made from a weak acid salt of the amine where the weak acid could precipitate on the surface of the pellet. A dramatic effect of *p*H was reported (O'Reilly *et al.* 1966) for the dissolution of a commercial tablet containing sodium warfarin (tablet A) and an experimental tablet containing warfarin acid (tablet D). While tablet A dissolved 350 times more rapidly than tablet D in water, tablet D dissolved 14 times more rapidly than tablet A in *p*H 7.4 buffer after exposure of both tablets to 0.1 N hydrochloric acid for 30 minutes. This study strongly suggested that for many tablets there must be a preliminary exposure to highly acidic media in dissolution rate tests to obtain data which will correlate with *in vivo* absorption rate.

The interdependence of physiologic surfactant and drug particle size with dissolution behavior of water-insoluble drugs was shown by Lin *et al.* (1968). In the presence of 0.5 percent aqueous lysolecithin, a naturally-occurring biosurfactant, the asymptotic concentration of diuretic compound A was about five times the concentration attained in water when micronized powder was employed but only about three times the concentration attained in water when 60/80 mesh powder or 12/16 mesh powder was tested. *In water alone,* the dissolution rate profiles showed that the micronized powder dissolved *more slowly* than the

*See citations in Chronological Bibliography, page 133.

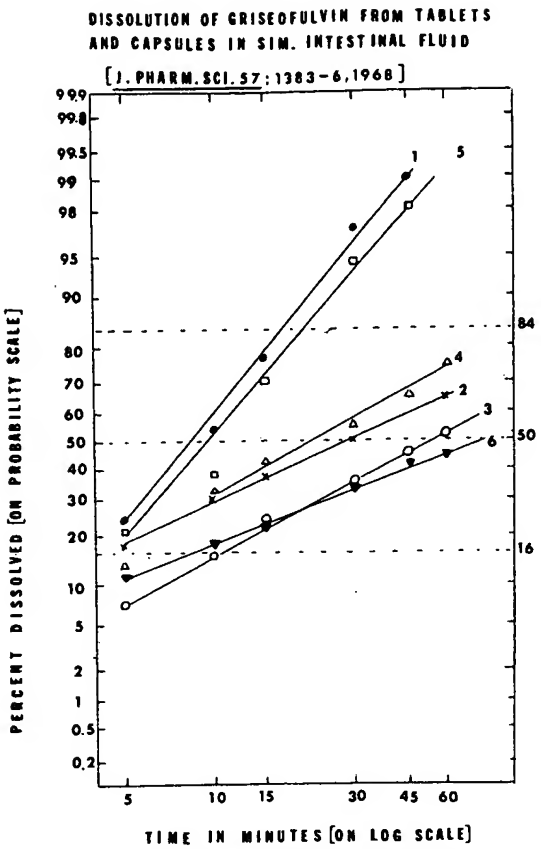


Figure 18.1. Dissolution data, from six different griseofulvin preparations tested *in vitro* in simulated intestinal fluid, are plotted on logarithmic probability graph paper. [Data from Symchowicz and Katchen (1968) plotted according to the method of Wagner (1969)]

60/80 or 12/16 mesh powders due probably to aggregates formed by the electrostatic charge acquired during micronization. The surfactant apparently wet the hydrophobic surface and broke up the aggregates. With glutethimide the rate of dissolution at first increased with decrease in particle size, then decreased with further decrease in particle size. Griseofulvin, whose solubility in 0.05 percent aqueous lysolecithin (0.024 percent) is 70 percent higher than in water (Bates *et al.*, 1966), exhibits particle size effects on blood levels achieved *in vivo*. Lin *et al.* (1968) concluded that the higher the extent of interaction between the drug and the biosurfactant the greater the dependency of drug concentration in the blood on the particle size of the drug.

The surface tension of the dissolution medium was shown to have an appreciable effect on the dissolution kinetics of phenacetin and phenobarbital (Finholt and Solvang, 1968). They showed that the effect of polysorbate 80 on the rate of dissolution of phenacetin in 0.1 N hydrochloric acid-polysorbate 80 solution was due only to a small extent on the solubilizing power of polysorbate 80 for phenacetin, but that the effect of the surfactant was mainly due to its ability to decrease the interfacial tension between phenacetin and the dissolution medium. The rate of dissolution of phenacetin in diluted human gastric juice increased with decrease in particle size, whereas the opposite was the case for phenacetin dissolving in 0.1 N hydrochloric acid. Also, phenacetin of all particle sizes dissolved much more rapidly in diluted human gastric juice than it did in 0.1 N hydrochloric acid. The rate of dissolution of phenacetin in polysorbate 80-0.1 N hydrochloric acid solutions, adjusted to the same *p*H and surface tension as diluted human gastric juice, was essentially the same as the rate of dissolution of the drug in similar particle size in diluted human gastric juice. When dissolution of sodium phenobarbital was studied in 0.035 N hydrochloric acid and in diluted gastric juice the precipitation of phenobarbital in excess of solubility took place much more slowly in diluted human gastric juice than in plain hydrochloric acid solution. Human gastric juice obviously contains one or more substances which retard precipitation of the free acid form of the drug.

When phenobarbital tablets were formulated with 1 percent ethylcellulose as binder it took 60 minutes to release 98 percent of the drug in 0.1 N hydrochloric acid as measured in a dissolution test but the same tablets disintegrated in water in ½ minute. This great disparity was attributed to the fact that the tablets swelled in contact with water and broke apart into small particles, whereas in the acidic medium no such swelling was observed (Jacob and Plein, 1968).

Singh *et al.* (1968) studied the role of wetting on rate of drug release from inert matrices. They showed that both matrix permeability and rate of permeation of the matrix by the solvent can individually limit drug release rates. This was found to be a function of the pore size distribution of the matrix and the permeation pressure of the release media as defined by its surface tension and contact angle.

An investigation of filler-binder, lubricant, disintegrating agent and hardness on the dissolution rate of sodium salicylate from tablets was studied by means of a 4x3x2x2 factorial experiment and analysis of variance (Marlowe and Shangraw, 1967). It was found that the release of sodium salicylate from the tablets was a result of the interaction of many variables and was not dependent solely on the effect of an individual component.

Nelson (1958) studied the rates of dissolution of mixtures of weak acids (benzoic acid, theophylline, theobromine and phenobarbital) and tribasic sodium phosphate. In general, incorporation of tribasic sodium phosphate with the weak acid increased the rate of dissolution of the weak acid but the composition giving the maximum rate of dissolution was different for each of the weak acids studied. W. I. Higuchi *et al.* (1965) developed a theory for the dissolution rate of such polyphase mixtures based on a diffusion-controlled process. It is surprising to the author that the empirical observations of Nelson (1958) and the theory developed by W. I. Higuchi *et al.* (1968) do not ap-

pear to have been applied very widely in practical tablet and capsule formulations of weak acids.

Relative intensity of agitation is extremely important in dissolution rate testing. One must be in the correct range of *in vitro* intensities in order to obtain data which will correlate with *in vivo* results. This was first clearly shown using compressed disks of methylprednisolone, polymorphs I and II, by Hamlin *et al.* (1962). Data calculated from their figures are shown in Table 18.1

Table 18.1. Ratios of Rates of Dissolution for Methylprednisolone Polymorphs I and II

RATIO OF RATE OF DISSOLUTION OF POLYMORPH II (MG/CM²/HR) TO RATE OF DISSOLUTION OF POLYMORPH I (MG/CM²/HR)	
Pellet implant in rats	1.69
Static hanging pellet method	1.53
Pellet holder method, Wruble machine, 6 r.p.m.	1.31
Pellet holder method, machine of Souder and Ellenbogen, 40 r.p.m.	1.04
Pellet holder method, Wruble machine, 12 r.p.m.	1.00

In this case the static hanging pellet method *in vitro* gave results correlating most closely with the ratio of rates observed from pellet implants in rats. When the intensity of agitation was increased the ratio of rates decreased until the ratio was unity (corresponding to equal dissolution rates) when the pellets were agitated at 12 r.p.m. in the Wruble apparatus.

When correlations are made between *in vitro* dissolution rate results and results obtained in man after *oral* administration of dosage forms the relationships are different. As pointed out formerly, Levy and Hollister (1965), employing the beaker method of Levy and Hayes (1960), found that the range of individual absorption half-times (0.70 to 1.9 hours) of acetylsalicylic acid in various solid oral dosage forms fell in the range of *in vitro* dissolution half-times obtained by using agitation intensities from 30 to 60 r.p.m. (0.6 to 2.3 hours). The mean absorption half-time in man (1.3 hours) was equivalent to the *in vitro* dissolution half-time obtained by using a rotational speed of 50 r.p.m. in that procedure.

Uniform Dissolution Rate Tests

It is obvious from the above that we must be very cautious in: (a) applying some uniform dissolution rate test to tablets and capsules of some drug not hitherto studied in a system, and, (b) applying specifications for *in vitro* dissolution rate test results to a new tablet or capsule of a drug studied in a system where the specifications were established by an *in vitro-in vivo* correlation employing different types of tablets or capsules containing the same drug. The *in vitro* test conditions which give results which correlate well with *in vivo* results may be different for different drugs and even for different tablets or capsules containing the same drug. It is feasible to design conditions of an *in vitro* dissolution rate test which will give results correlating with *in vivo* results for a wide variety of tablets and capsules containing the same drug. But each drug must be separately studied. Test conditions established for even a large number of drugs cannot be just blindly applied to a new drug and its dosage forms not hithertofore studied in that system.

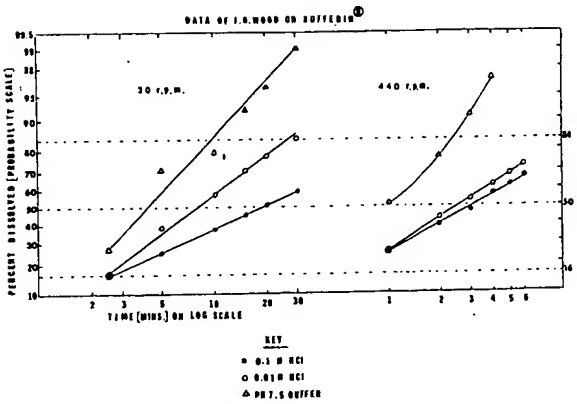


Figure 18.2. Dissolution of aspirin from Bufferin in 0.1 N hydrochloric acid, 0.01 N hydrochloric acid and pH 7.5 buffer at slow (30 r.p.m.) and fast (440 r.p.m.) stirring speeds. [Data from Wood (1966) plotted according to the method of Wagner (1969)] Note that in five out of six cases this method of plotting linearizes the percentage dissolved, time data. In one case (pH 7.5 buffer at 440 r.p.m.) the line is curved on this plot but the data are linearized by first order method of plotting (see Figure 18.3.).

Interpretation of Dissolution Rate Data from in Vitro Testing of Tablets and Capsules

Surface Area Concept

Under sink conditions a percent dissolved value at time t may simply be equivalent to the percent surface area generated to time t (Wagner, 1969).* This may be shown as follows. Under sink conditions (*i.e.*, $C << C_s$, usually $C \leq 0.1\ C_s$) Equation 18.1 may be expected to apply during the dissolution process.

$$\frac{dW}{dt} = KSC_s \qquad \text{Eq. 18.1}$$

where $\frac{dW}{dt}$ is the rate of dissolution, K is a constant with dimensions of length/time, S is the surface area with dimension of length^2 and C_s is the solubility of the drug in the dissolution medium.

*The abstract formerly cited has been published as Interpretation of Percent Dissolved Time Plots Derived from in Vitro Testing of Conventional Tablets and Capsules, *J. Pharm. Sci.* 58:1253-1257, 1969.

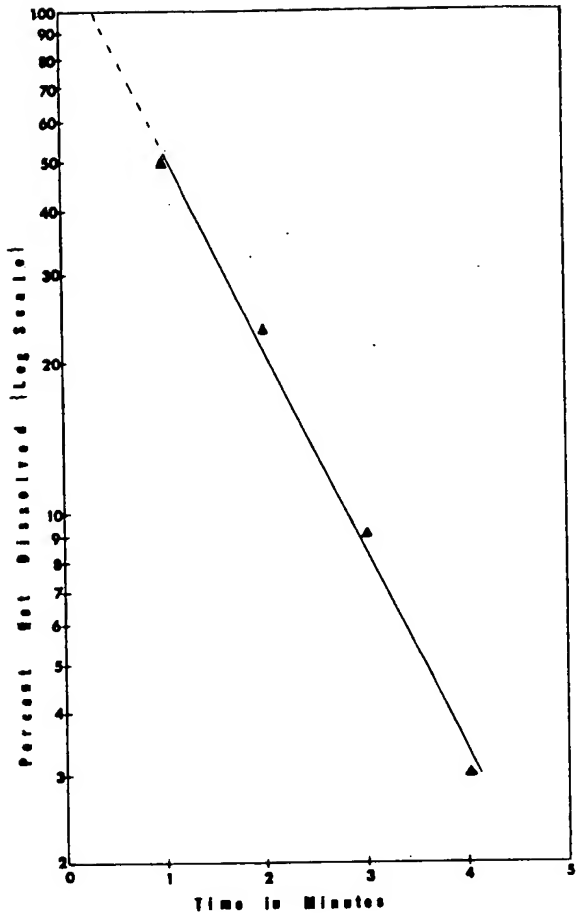


Figure 18.3. Data of Wood (1966) on dissolution of aspirin from Bufferin in pH 7.5 buffer at fast stirring speed (440 r.p.m.) plotted in first order fashion. These are the same data that give the curved line in Figure 18.2.

Integration of Equation 18.1. between the limits $t = o$ and $t = T$, where T is some particular time during the dissolution process, yields Equation 18.2.

$$W = KC_s \int_o^T S(t)dt \qquad \text{Eq. 18.2}$$

where W is the cumulative amount dissolved to time T and the integral represents the cumulative surface area which has been made available for dissolution from time zero to the particular time T. By analogy, at infinite time, we obtain Equation 18.3:

$$W^\infty = KC_s \int_o^\infty S(t)dt \qquad \text{Eq. 18.3}$$

where W^∞ represents the amount in solution at infinite time and the integral represents the total surface area of drug which has been made available for dissolution during the test. In practice, a dissolution rate test may be run with a constant stirrer speed until say, 90 percent of the drug has dissolved then the stirrer speed is increased markedly until all the drug in the original dosage form has been dissolved to estimate W^∞

Division of Equation 18.2 by Equation 18.3 yields Equation 18.4

$$\begin{aligned}\%\text{ dissolved to time t} &= \frac{W}{W^\infty} \times 100 = \frac{\int_o^T S(t)dt}{\int_o^\infty S(t)dt} \times 100 \\ &= \%\text{ surface area generated to time T of total surface area generated}\end{aligned} \qquad \text{Eq.18.4}$$

If Equation 18.4. is valid, then percent dissolved, time data derived from *in vitro* testing of tablets and capsules may best be described by a distribution function, such as the logarithmic-normal or logarithmic-logistic distribution functions, and the parameters of the distribution employed to describe the data. If dissolution data follow a logarithmic normal distribution then one expects a single linear trend line when the percent-dissolved values are plotted on the probability scale (ordinate) against the time values on the logarithmic scale (abscissa) of logarithmic-normal (or probit) graph paper. Two examples are shown in Figures 18.1 and 18.2. It was shown by Wagner (1969) that data generated by the log-normal distribution function could be interpreted according to first order kinetics but in such cases the first order plots were really artifacts.

First Order Kinetics

There are two approaches to deriving a first order rate equation in the case of *in vitro* dissolution kinetics under sink conditions. The first method is that of Wagner (1969).

(1) For the case when there are sink conditions and surface area varies with time, one may assume that during some part of the dissolution process the surface area available for dissolution decreases exponentially with time in accordance with Equation 18.5.

$$S = S^o e^{-k_s(t-t_o)} \qquad \text{Eq. 18.5}$$

where S^o is the surface area which is available for dissolution at the time when the apparent first order dissolution phase commences at time t_o. Substitution of Equation 18.5 into Equation 18.1 yields Equation 18.6.

$$\frac{dW}{dt} = KC_s S^o e^{-k_s(t-t_o)} \text{ for } t \geq t_o \qquad \text{Eq. 18.6}$$

Integration of Equation 18.6 yields Equations 18.7 and 18.8.

$$W = W_{t_o} + \frac{K}{k_s} \cdot C_s \cdot S^o \left[1-e^{-k_s (t-t_o)}\right] \text{ for } t \geq t_o \qquad \text{Eq. 18.7}$$

or,

$$W = W_{t_o} + M \left[1-e^{-k_s (t-t_o)}\right] \text{ for } t \geq t_o \qquad \text{Eq. 18.8}$$

where W_{t_o} is the amount dissolved to time t_o and $M = \frac{K}{k_s} \cdot C_s \cdot S^o$ and has dimension of mass. Since $W^\infty = W_{t_o} + M$, we can rearrange Equation 18.8 to

$$W^\infty - W = Me^{-k_s (t-t_o)} \text{ for } t \geq t_o \qquad \text{Eq. 18.9}$$

Taking logarithms of both sides of Equation 18.9 gives Equation 18.10.

$$\log (W^\infty - W) = \log M - \frac{k_s}{2.303} (t-t_o) \text{ for } t \geq t_o \qquad \text{Eq. 18.10}$$

where $W^\infty - W$ is the amount not dissolved from the dosage form. This derivation provides a basis for dissolution data obeying first order kinetics since Equation 18.10 is a first order rate expression.

(2) Assume that the effective surface area available for dissolution, S, at any time t is proportional to the amount of undissolved drug. That is,

$$S = k'(W^\infty - W) \qquad \text{Eq. 18.11}$$

where k′ is a proportionality constant with dimensions of length²/mass.

Substituting for S in Equation 18.1 from Equation 18.11 yields

$$\frac{dW}{dt} = KC_s k' (W^\infty - W) \qquad \text{Eq. 18.12}$$

Equation 18.12 may be written as Equation 18.13.

$$\frac{dW}{dt} = k (W^\infty - W) \qquad \text{Eq. 18.13}$$

where $k = KC_s k'$ and has dimensions of 1/time.

Integration of Equation 18.13 gives

$$\log (W^\infty - W) = \log W^\infty - \frac{k}{2.303} t \qquad \text{Eq. 18.14}$$

An analogous derivation of this first order rate equation was given by Gibaldi and Feldman (1967)* where $(W^\infty - W)$ was assigned the symbol A and W^∞ was assigned the symbol A^∞.

Second Order Kinetics

Both Gibaldi and Feldman (1967)* and Raghunathan and Becker (1968) showed how, under special non-sink conditions, one can obtain second order *in vitro* dissolution kinetics.

Exponential Release

Wiseman and Federici (1968) published linear plots of percent aspirin released on the logarithmic scale of semilogarithmic graph paper *versus* time in hours for the release of aspirin from various matrices in tablet form. This indicates exponential release of the growth type with the equation describing such data being of the form of Equation 18.15.

$$R = R_o \cdot e^{k(t-t_o)} \qquad \text{Eq. 18.15}$$

where R is the percent released, R_o is the amount which has been released at the time t_o when the exponential release began, k is a constant and t is the time.

Square Root of Time Plots

Diffusion-controlled drug release when the drug is dispersed as a solid in a matrix has been studied by T. Higuchi (1963) and W. I. Higuchi *et al.* (1965 to 1969). If the matrix is homogeneous, planar diffusion to a perfect sink leads to Equation 18.16.

$$Q = \sqrt{D(2A-C_s)C_s t} \qquad \text{Eq. 18.16}$$

where Q is the amount of drug released per unit surface area, D is the drug molecule diffusion coefficient in the matrix, A is the total amount of drug in the matrix per unit volume, C_s is the solubility of the drug in the matrix substance and t is the time.

If the matrix is heterogeneous and diffusion takes place in the intergranular pores (*i.e.*, drug is dispersed in an inert plastic matrix with aqueous pores) one obtains Equation 18.17.

$$Q = \sqrt{\frac{DE}{\tau}(2A-EC_s)C_s t} \qquad \text{Eq. 18.17}$$

where D is the diffusion coefficient of the drug molecule in the solvent, E is the porosity of the matrix, τ is the tortuosity of the matrix and Q, A, C_s and t have the meanings assigned above.

For both of these cases a plot of Q *versus* the square root of time will be linear. Desai *et al.* (1965, 1966) have shown such matrices yield linear square root of time plots.

*Gibaldi, M. and Feldman, S.: Establishment of Sink Conditions in Dissolution Rate Determination. Theoretical Considerations and Application to Nondisintegration Dosage Forms, *J. Pharm. Sci.* 56:1238-1242, 1967.

CHAPTER 19

Theoretical and Practical Considerations in Correlation of in Vivo Data with in Vitro Rate of Dissolution Data

Theory of Correlation of in Vivo with in Vitro Data

WE MAY DEFINE MEASUREMENT AS THE ASSIGNMENT OF numerical values to observations in such a way that these values can be manipulated according to certain rules. The rules which are pertinent depend upon the level of measurement being used.

Levels of Measurement

Four levels or types of scales will be presented in order from the lowest to the highest level.

(1) *Nominal.* This is a subgrouping of objects into separate classes such that all objects in the same class are equivalent according to some criteria, but objects in different classes are unequal with respect to the particular criterion. There is no numerical basis to this measure and therefore arithmetical procedures are not allowable. This type is often called classifying rather than measuring. Examples are measuring sex as male or female, race as white or non-white, etc.

(2) *Ordinal.* This is a ranking procedure in which one can define not only equality and inequality but also greater or less than. The magnitude of the distance or amount between the values is not defined but the relationship between the values is defined. Examples are: (a) grading of heart disease according to criteria set up by the Heart Association, *i.e.*, Class I = mild improvement up to Class IV = symptoms even at rest; (b) grading of pain relief due to an analgetic by a set such as 4,3,2,1,0 where the degree of relief between assigned values of 4 and 3 is not necessarily the same as the degree of relief between 1 and 0. Most sets of clinical observations are of this type.

(3) *Interval Scale.* In this type of measurement the numbers assigned are such that there are equal distances or amounts between values of the measurement scale. An example is Fahrenheit degrees as a measure of temperature; temperatures of two people of 99° and 100° differ by an equal amount, namely 1°, to temperatures of two people of 98° and 99°. It should be noted that with interval scales zero does not mean the absence of the quantity being measured. In the Fahrenheit temperature scale zero does not mean the abscence of heat. Also ratios are not comparable. For example, 2°F/1°F does not mean the same thing as 64°F/32°F.

(4) *Ratio Scale.* This is like an interval scale but with zero measuring complete absence of the measured quantity and ratios actually measure proportionate changes in the measured quantity. For example, the Kelvin scale of temperature has its zero where heat is absent. Objects at a temperature of 2°K are twice as hot as objects at 1°K.

Types of Correlations

There are two basic types of correlations we may consider. These are as follows:

A *quantitative correlation* is one where the *in vivo* variable Y is related to the *in vitro* variable X by an

equation as $Y = b \cdot X$, $Y = a + bX$, $\log Y = \log Y^{\circ} - bX$, etc. These are obviously the more informative type. However, such a relationship should probably be derived only when there is a theroetical reason for relating the variables as indicated by the equation derived. Only variables definable by an interval scale or a ratio scale should be correlated in this manner. Pearson's product moment correlation (Pearson's r) is most widely used to test the significance of such a correlation. Here r, often called the correlation coefficient, is obtained by application of the formula:

$$r = \frac{\Sigma XY - \frac{\Sigma X \Sigma Y}{N}}{\left(\Sigma X^2 - \frac{(\Sigma X)^2}{N}\right)^{1/2}\left(\Sigma Y^2 - \frac{(\Sigma Y)^2}{N}\right)^{1/2}} \qquad \text{Eq. 19.1}$$

In practice, one calculates the value of r from a set of data and compares the calculated value to tabled values of r to obtain the level of significance of the correlation. However, one may have a highly significant correlation yet the correlation be very poor for predictive purposes. The quantity, r^2, is called the coefficient of determination. The quantity 100 r^2 is the percent of the variance of the Y values which may be accounted for by the difference in the X values for a regression of the type $Y = a + bX$. Unless the 100 r^2 value is very large (of the order of 90 to 100) then the relationship established will not be very good for predictive purposes. If the 100 r^2 value is small (much less than 100) then the confidence limits of a predicted Y value will be large for a given X value. Due to the wide variability in *in vivo* variables (Y) it is often extremely difficult to obtain *in vivo-in vitro* correlations with very high 100 r^2 values. Yet the setting of *in vitro* dissolution rate specifications really should depend upon such a correlation. In the process of setting *in vitro* specifications good statistical techniques should be applied to determine the validity of the specifications chosen.

A *rank order correlation* is one in which (a) Y increases as X increases, (b) Y increases as X decreases or (c) Y decreases as X increases. A variable definable by an ordinal measurement may be rank order correlated with another variable definable by an ordinal measurement. Or, variables which are definable by an interval scale or ratio scale may be transformed to rank order forms and then the ranks treated statistically. Consider Table 19.1.

Table 19.1. Examples of Rank Order Correlations

A "PERFECT" RANK ORDER CORRELATION		AN "IMPERFECT" RANK ORDER CORRELATION	
X	Y	X	Y
3	1	3	1
5	2	7	2
7	3	5	3
9	4	9	4
11	5	11	5

In Table 19.1 the numbers listed refer to the actual values of the variables measured. If we assign ranks to the numbers by assigning number 1 to the lowest and number 5 to the highest value in each set then we obtain the ranks shown in Table 19.2.

Table 19.2. Ranks from Data in Table 21.1.

A "PERFECT" RANK ORDER CORRELATION		AN "IMPERFECT" RANK ORDER CORRELATION	
X	Y	X	Y
1	1	1	1
2	2	3	2
3	3	2	3
4	4	4	4
5	5	5	5

Note that for the set in the left of Table 19.2 X and Y pairs are always the same hence it is called a "perfect" rank order correlation. For the set in the right there is a "reversal" in the second and third pairs. For rank order correlations one should make a statistical test such as Spearman's Rank Order Correlation (Rho) which may be found in any standard statistics textbook.

Variables Derived from in Vivo Data Which Have Been Correlated with Variables Derived from in Vitro Data

(1) Blood (plasma or serum) concentration-time plot or the corresponding numerical values.

(2) Peak blood (plasma or serum) concentrations.

(3) Area under the blood (plasma or serum) concentration curve in some interval such as T_1 to T_2 hours.

(4) Area under the blood (plasma or serum) concentration curve over observation period (0 to T hours where T is the last time a blood sample was taken) after a single dose of drug.

(5) Estimated area under the blood (plasma or serum) concentration curve from zero to infinite time after a single dose of drug, or the area in a dosage interval at the equilibrium state after multiple doses of drug.

(6) Rate constant for absorption or the half-absorption time derived by applying a pharmacokinetic model to blood (plasma or serum) concentration or urinary excretion data.

(7) Amount of drug excreted in the urine in a given time.

(8) A plot of cumulative amount of drug excreted *versus* time.

(9) Urinary excretion rates at given times.

(10) Percent absorbed-time plots derived by pharmacokinetic analysis of blood (plasma or serum) concentration or urinary excretion data.

(11) Amount of drug absorbed per milliliter of the volume of distribution which is estimated by pharmacokinetic analysis of data by several methods.

(12) Pharmacological responses such as blood sugar lowering, blood pressure, pain relief, etc.

Table 19.3. Hypothetical Example of *in Vitro* $t_{80\%}$ Values and Half-Absorption Times *in Vivo*

TABLET	IN VITRO $t_{80\%}$ (HRS)	ESTIMATED HALF-ABSORPTION TIME IN VIVO (HRS)	IN VIVO / IN VITRO RATIO
P	1	2	2
Q	½	1	2
Ratio of Q/P	½	½	

Variables Derived from in Vitro Data Which Have Been Correlated with Variables Derived from in Vivo Data

(1) Disintegration time.

(2) Time for some percentage of the drug to dissolve *in vitro*. For example, $t_{20\%}$ — time for 20 percent of the drug to dissolve and $t_{50\%}$ — time for 50 percent of the drug to dissolve.

(3) Concentration of solution or amount in solution at a given time.

(4) Percent dissolved-time plots

(5) Rate of dissolution *versus* time plots

(6) First order plot of percent not dissolved on logarithmic scale *versus* time in hours.

(7) Logarithmic probability plots of percent dissolved on probability scale *versus* time on logarithmic scale.

(8) Rate constants or half-dissolution times derived from a first order plot or plots appropriate to other types of kinetics.

(9) Intrinsic rates of dissolution.

Which Variables Should Be Correlated?

The time for 50 percent of the drug to dissolve *in vitro* ($t_{50\%}$) is probably the best *in vitro* variable to correlate since: (1) its value indicates the central tendency of the *in vitro* dissolution data and (2) by use of this value one has not committed oneself to any formal kinetic interpretation of the data.

Optimally, if absorption is dissolution-rate controlled *in vivo*, the best number to estimate from *in vivo* data, such as plasma concentration or urinary excretion data, is the time for 50 percent of the drug to be absorbed (*i.e.*, the half-absorption time). The absolute value of the half-absorption time one estimates from plasma concentration data depends upon the pharmacokinetic model one employs in the estimation. However, using simulated data the author has recently shown that even though the absolute values of the half-absorption times may be in error their ratios are nearly correct even if the wrong pharmacokinetic model is employed. *Hence, with the present state of the art the most accurate manner of relating in vitro and in vivo data of the dissolution type appears to be the correlation or comparison of ratios of half-absorption times estimated from plasma concentration data with the ratios of in vitro* $t_{50\%}$ *values*. Let's assume that the data shown in Table 19.3 were collected for two tablets P and Q. Then these data constitute an excellent correlation between *in vitro* and *in vitro* results.

It is assumed that in deriving the numbers entered in a table such as Table 19.3 a sufficient number of tablets were tested *in vitro* and a sufficient number of subjects were employed in *in vivo* studies to establish highly significant differences between the *in vitro* $t_{50\%}$ and *in vivo* half-absoption times listed for tablets P and Q. In many of the *in vitro-in vivo* correlations reported in the literature this has not always been the case.

Relative efficiency of absorption following equal doses, may be defined as in Equation 19.2.

$$\text{Relative efficiency of absorption} = \frac{\text{Amount absorbed from one preparation}}{\text{Amount absorbed from another preparation}} \times 100 \qquad \text{Eq. 19.2}$$

When the denominator of Equation 19.2 is derived from an aqueous solution, or a very rapidly available preparation giving results comparable to an aqueous solution (called the standard), then the relative efficiency of absorption of the test preparation is called its physiological availability.

$$\text{Physiological availability of test preparation} = \frac{\text{Amount absorbed from test preparation}}{\text{Amount absorbed from the standard}} \times 100 \qquad \text{Eq. 19.3}$$

What are the appropriate numbers to put in the denominator and numerator of Equation 19.2 and 19.3 to represent "amount absorbed"? The difficulty is that there are several answers and each involves a different assumption or set of assumptions. Some of these are discussed below.

Parameters Which May Be Used to Estimate "Amount Absorbed" from Plasma Concentration Data

(1) The estimated area under the plasma concentration curve *from zero to infinite time* after a single dose of drug, or the area in a dosage interval at the equilibrium state when multiple doses of drug are given at uniform time intervals. Use of either of these areas involves the assumption that the plasma clearance of drug is the same following the two treatments. In terms of a conventional pharmacokinetic model the plasma clearance of a drug is the product of the entire or partial volume of distribution (*i.e.*, the volume of the compartment under consideration) and the first order rate constant for elimination of drug by all

processes from that compartment. The plasma clearance has dimensions of volume/time.

(2) The amount of drug absorbed per milliliter of the volume of distribution, *i.e.*, FD/V in terms of the one compartment open model or FD/V_1 in terms of the two compartment open model. In terms of the one compartment open model FD/V is equivalent to the product of the first order elimination rate constant and the area $0 \rightarrow \infty$ after a single dose of drug or the area in a dosage interval at the equilibrium state after multiple doses of drug given at uniform time intervals. Use of this parameter to estimate "amount absorbed" involves the assumptions that (1) the volume of distribution of drug is the same following the two treatments and (2) estimation of the elimination rate constants after the two treatments has not been biased by measurement in a region where absorption is still proceeding but that when the elimination rate constant is estimated absorption has ceased. Use of this parameter does allow for differences in the elimination rate constant when two treatments were administered. Such differences in elimination rate constants in the same subject from time to time of administration do occur.

(3) The C° or partial coefficient of exponential terms derived from nonlinear least squares fitting of plasma concentration data. This has concentration units and is analogous to FD/V or FD/V_1 above but is derived in different manner.

Parameters Which May Be Used to Estimate "Amount Absorbed" from Urinary Excretion Data

(1) Total amount of unchanged drug excreted into urine in infinite time (usually taken as 10 elimination half-lives of the drug) following a single dose of drug.

(2) Amount of unchanged drug excreted in a dosage interval at the equilibrium state after multiple doses of drug given at uniform time intervals.

Use of both of these involves the assumption that the fraction of drug reaching the circulation which is excreted unchanged in the urine is the same following both treatments.

Inappropriate Variables. It should be noted that the variables cited above are those which are meaningful in terms of pharmacokinetic theory. It is inappropriate to estimate relative absorption or physiological availability with parameters such as amount excreted in T hours when T is equal to less than about 10 half-lives of the drug or area under the plasma concentration curve from 1 to 8 hours or 0 to 8 hours when the plasma concentration is elevated and measurable following one or both treatments at the end of 8 hours. Unfortunately many correlations of *in vivo* with *in vitro* data have employed such inappropriate parameters derived from *in vivo* data. In such cases the correlation may or may not be valid.

Rank Order Correlations of in Vivo with in Vitro Variables

There are many possibilities for rank order correlations of *in vivo* with *in vitro* variables. For example, relative efficiency of absorption in dissolution rate-controlled absorption may be expected to rank order correlate with an *in vitro* variable such as $t_{50\%}$ *in a certain range of* $t_{50\%}$ *values*. Below a certain critical $t_{50\%}$ value (peculiar to the drug and dosage forms studied) one would expect relative absorption efficiency to be 100 (*i.e.*, equal amounts absorbed following two treatments). However, once the critical $t_{50\%}$ is exceeded one may expect a rank order correlation between relative absorption efficiency and $t_{50\%}$. Due to many complicating factors usually one may not expect to derive a quantitative correlation equation relating relative absorption efficiency and a parameter such as $t_{50\%}$.

Peak plasma concentration may also be rank correlated with a variable such as $t_{50\%}$ derived from *in vitro* testing. This may be expected since there is often a high degree of correlation between peak level and total area under the plasma concentration curve. Another interesting point is as follows. If an author reports a high degree of correlation between a pharmacological response and peak plasma or serum concentration one *cannot* conclude that only the peak level is related to activity of drug. Since the peak level and integral (*i.e.*, total area) are often so highly correlated one really cannot decide, on this type of data, that the response was due to the peak level or to the entire exposure to varying plasma concentrations.

What Is Needed in Biopharmaceutics

Biopharmaceutics needs quantitative correlations of appropriate variables derived from *in vivo* testing in human volunteers with appropriate variables derived from *in vitro* dissolution rate tests. Despite the large amount of investigation carried out in recent years there are still very few good correlations existing in the literature. The human studies must be performed with sufficient subjects that appropriate statistical procedures may be applied to the data collected. The application of the statistical procedures should show significant differences between or among treatment averages and illustrate that correlations of *in vivo* with *in vitro* data have predictive value. Studies must be designed with the statistical procedures, later to be applied to the data in mind when the protocol is written. When one or more authors do report a good correlation between an appropriate *in vivo* variable and a variable derived from an established *in vitro* rate of dissolution test this should be followed up by other investigators employing the same *in vitro* test. The ceaseless modification of *in vitro* dissolution rate testing equipment has to stop at some point. We must determine, *at sometime*, whether we have a reasonably good piece of apparatus in our armamentarium at present and perform studies to prove or disprove its usefulness.

CHAPTER 20

Rank Order Correlations of in Vivo Data with in Vitro Rate of Dissolution Data

THE RATE AT WHICH A DRUG DISSOLVES FROM ITS INTACT or fragmented dosage forms in the human gastrointestinal, or in a parenteral injection site, often partially or completely controls the rate at which the drug appears in blood (*i.e.*, the rate of absorption) and the rate of urinary excretion of the drug. Results of *in vitro* rate of dissolution tests may often be correlated with *in vivo* results obtained with the same dosage forms. This section is concerned with examples of rank-order correlations of *in vivo* results with *in vitro* results where dissolution rate appears to be the rate-determining factor.

Tetracycline

(1) Doses of 200 mg of tetracycline hydrochloride activity were administered to human subjects in the form of two pellets (0.95 cm diameter and 0.15 cm thick, pressed at a pressure of 1000 Kg/cm^2) packed in a 000 capsule with 200 mg of sodium bicarbonate. Four different forms of tetracycline were employed.

In vitro rate of dissolution tests were performed by the hanging pellet method using the same type of pellets as ingested by the human subjects. Data, reported by Nelson (1959) are summarized in Table 20.1.

Table 20.1. Rank Order Correlation of Urinary Excretion of Tetracycline Hydrochloride Activity in Man with *in Vitro* Rate of Dissolution (Data from Nelson, 1959)

FORM	NO. SUBJECTS	AVERAGE AMOUNT (MG) EXCRETED TO TIME INDICATED			*In Vitro* RATE OF DISSOLUTION (MG/CM²/HR)		
		1 HR.	2 HR.	3 HR.	GASTRIC FLUID	NEUTRAL INTESTINAL FLUID	ALKALINE INTESTINAL FLUID
Tetracycline	10[a]	0.2	1.5	3.3	2.6	<.001	<.001
Tetracycline phenolsulfonphthaleinate	10[a]	0.5	3.5	7.7	0.12	0.09	3.0
Tetracycline sodium hexa-metaphosphate complex	6[b]	1.1	5.3	10.4	6.1	1.7	26.
Tetracycline hydrochloride	6[b]	3.0	12.0	20.4	4.1	7.8	38.

[a] - Same 10 subjects
[b] - Same 6 subjects, which were included in the panel of 10 subjects above.

(2) Doses of 250 mg of tetracycline hydrochloride activity were administered as tetracycline hydrochloride in capsules made by four different manufacturers in a crossover study in 12 adult male volunteers. Blood samples were taken at 0, ½, 1, 2, 3 and 6 hours and all urine voided for the first 8 hours was collected. Serum and urine samples were analyzed, under code, by microbiological methods. *In vitro* rate of dissolution tests were performed in a special V-shaped, transparent plastic cylindrical chamber which oscillated freely about its center. The dissolution medium was a *p*H 1.0 simulated gastric fluid maintained at 37°C. Data reported by Macdonald, *et al.* (1969)** are shown in columns 1, 2, 4, 5,6,7,8,9 and 12 of Table 20.2.

The numbers shown in columns 3, 10, 11 and 13 of Table 20.2 were calculated by the author. The areas under the average serum concentration curves were estimated by means of the trapezoidal rule. The relative area and relative urinary excretion values were calculated from the areas and urinary excretion, respectively. The reciprocals of the $t_{50\%}$ values should yield an estimate of the relative *in vitro* rates of dissolution of tetracycline hydrochloride from the various capsules. These reciprocals were calculated then the relative values calculated; these are shown in column 3 of Table 20.2. It should be noted that the relative areas and relative urinary excretion values for the four preparations agree quite well. Also, the relative *in vitro* $1/t_{50\%}$ values are rank-order correlated with both the relative areas and relative urinary excretion values. There is nearly a linear relationship between the relative areas (or relative urinary excretion) and the logarithms of the relative $1/t_{50\%}$ values.

Tolbutamide

(1) The absorption of tolbutamide from compressed disks of the free acid and three of its salts in four adult volunteers by measurement of the urinary excretion of metabolites, the blood sugar lowering effects of the same disks in 23 normal volunteers, and *in vitro* rates of dissolution of tolbutamide from the disks by the hanging pellet method were studied by Nelson, *et al.* (1962). The thin cylindrical disks of tolbutamide acid and the three salts of tolbutamide were 1.21 cm in diameter and their thickness varied from 0.168 cm to 0.225 cm, depending on the form of tolbutamide used. Each disk was compressed at 40,000 p.s.i., contained 250 ± 10 mg tolbutamide equivalent, and had a surface area of 3.38 ± 0.09 cm.² Two different panels of subjects were used.

One panel of four adult volunteers ingested the equivalent of 0.5 Gm tolbutamide on fasting stomachs and took no food until one hour post drug administration. Urine was collected quantitatively and analyzed for tolbutamide metabolites. The other panel of 23 normal subjects ingested 1.0 Gm of tolbutamide equivalent in the various forms at different times; drug was taken after an overnight fast and no food was taken during the course of the study (10 hours). Table 20.3 lists the urinary excretion results calculated from the data of Nelson, *et al.* (1962).

Table 20.2. Relationship Between Serum Concentrations and Urinary Excretion of Tetracycline Hydrochloride in Man and Results of an *in Vitro* Rate of Dissolution Test (Data from Macdonald *et al.*, 1969)**

PREP.	*In Vitro* $T_{50\%}$[c] (MINS.)	*In Vitro* RELATIVE $1/T_{50\%}$	AVERAGE SERUM CONCENTRATION (μG/ML) AT INDICATED TIME IN HOURS						AREA UNDER SERUM CURVE ($\frac{\mu G}{ML}$ X HRS.)	RELATIVE AREA	URINARY EXCRETION 0-8 HRS. (MG)	RELATIVE URINARY EXCRETION
			0	½	1	2	3	6				
A[a]	5.1	1.00	0	0.43	1.09	1.80	1.61	1.10	7.70	1.00	54.1	1.00
B[b]	41	0.12	0	0.27	0.78	1.28	1.19	0.83	5.63	0.73	38.5	0.71
C[b]	107	0.048	0	0.19	0.57	1.14	1.09	0.86	5.13	0.67	35.9	0.66
D[b]	244	0.021	0	0.08	0.29	0.76	0.69	0.53	3.19	0.41	22.2	0.41

[a] - Preparation A was Achromycin (Lederle Laboratories)
[b] - Preparations B, C and D were other commercial forms of tetracycline hydrochloride capsules.
[c] - Time for 50 percent of tetracycline hydrochloride to dissolve in *p*H 1.0 aqueous medium.

**For reference see page 132.

Table 20.3. Average Excretion of Metabolites of Tolbutamide in the Same Four Subjects After Administration of Two Disks Equivalent to 0.5 Gm Tolbutamide (Calculated from data of Nelson *et al.*, 1962)

FORM OF TOLBUTAMIDE	AVERAGE CUMULATIVE METABOLITES[a] EXCRETED (MG) TO HOUR INDICATED									
	1	2	3	4	6	8	10	12	24	48 HRS
1-Amino-2-propanol salt	19	65	113	166	241	297	343	380	504	557
Sodium salt	21	65	117	153	218	272	314	348	451	516
2-Amino-2-methyl-1-propanol salt	6	22	48	81	154	205	255	302	448	534
Tolbutamide (acid)	5	7	12	18	30	45	58	74	123	210

[a] - Calculated as carboxytolbutamide

The average differences in blood sugar in the 0-1 hour and 0-2 hour periods following oral administration of the equivalent of 1 gram of tolbutamide in the form of disks and the *in vitro* rates of dissolution of tolbutamide from the various disks are shown in Table 20.4.

The urinary excretion, blood sugar lowering and *in vitro* rates of dissolution rank-order correlate for the sodium salt, 2-amino-2-methyl-1-propanol salt and tolbutamide free acid in the form of compressed disks. Results for the 1-amino-2-propanol salt of tolbutamide did not correlate as well. Results obtained with the disks of tolbutamide (acid) in these studies should *not* be taken as indicative of results which are obtained with commercial tablets of tolbutamide. In these studies the surface area of tolbutamide was restricted to a very low value. The commercial tablets disintegrate in the gastrointestinal tract liberating drug in the fine particle size and results from such tablets are distinctly different.

(2) A correlation of the rate of decline of blood sugar levels in normal human subjects with the *in vitro* rate of dissolution of tolbutamide from three different solid oral dosage forms of tolbutamide and two solid oral dosage forms of its salts was reported by Wagner (1963). In the human studies 1 gram of tolbutamide or its equivalent was administered to a panel of subjects in a given form and, usually, 5 normal subjects received placebo. The zero hour blood sugar level was used as a covariate and adjusted average blood sugar levels as a percentage of the placebo group average were calculated from the blood sugar data at one hour post administration and at the nadir of the blood sugar curve. In the *in vitro* studies 1 gram of tolbutamide or its equivalent in a given solid form was tested in 750 ml of *p*H 7.2 THAM buffer using the U.S.P. disintegration apparatus. Samples were taken at intervals and assayed spectrophotometrically for tolbutamide. The rate constant reported is the slope of the initial linear segment of a plot of the natural logarithm of the percentage of tolbutamide not dissolved against time in minutes. Data are shown in Table 20.5.

Table 20.5. Rank Order Correlation of Adjusted Average Blood Sugar as a Percent of the Placebo Group Average in Normal Human Subjects with First Order Rate Constant for Dissolution *in Vitro* for Five Different Solid Oral Dosage Forms of Tolbutamide or its Salts (from Wagner, 1963)

SOLID ORAL DOSAGE FORM	ADJUSTED AVERAGE BLOOD SUGAR AS A % OF THE PLACEBO GROUP AVERAGE		IN VITRO RATE CONSTANT ($MINS.^{-1}$)
	AT 1 HOUR	AT THE NADIR	
1	96.1	95.0	0.011
2	94.4	87.2	0.024
3	83.2	82.2	0.23
4	79.2	79.2	0.32
5	73.9	73.9	2.3

The data of Table 20.5 indicate that the more rapidly the dosage form released tolbutamide *in vitro* (*i.e.*, the higher the *in vitro* rate constant for dissolution), the more rapid was the fall in blood sugar in normal human subjects as indicated by the adjusted average blood sugar levels at one hour and at the nadir.

Aspirin

(1) Ten grains (0.65 Gm) of aspirin in the form of two commercial tablets were swallowed whole, followed by 100 ml of water. In the case of the solution the volume was 100 ml. Doses were administered in the morning on

Table 20.4. The Average Differences in Blood Sugar in the 0-1 Hour and 0-2 Hour Periods in 23 Normal Volunteers After Single Oral Doses of 1 Gram Equivalent of Tolbutamide and the *in Vitro* Rates of Dissolution from the Disks by the Hanging Pellet Method (from Nelson *et al.*, 1962)

FORM OF TOLBUTAMIDE	DIFFERENCES IN BLOOD SUGAR LEVEL (MG%) IN 23 NORMAL VOLUNTEERS				IN VITRO RATE OF DISSOLUTION BY HANGING PELLET METHOD (MG TOLBUTAMIDE/CM^2/HR)	
	0-1 HOUR		0-2 HOUR			
	AVE.	S.E.[a]	AVE.	S.E.	0.1 N HCL.	PH 7.2 TRIS BUFFER
1-Amino-2-propanol salt	27.2	1.8	17.0	1.0	207	280
Sodium salt	19.1	2.3	23.7	1.8	1069	868
2-Amino-2-methyl-1-propanol salt	16.0	1.5	20.0	1.2	0.28	14
Tolbutamide (acid)	5.2	1.3	7.0	1.1	0.21	3.1

[a] - S.E.: Standard error of the average

Table 20.6. Milligrams of Apparent Salicylate Excreted in the Urine in One Hour and Amounts of Aspirin in Solution in 10 Minutes (Data of Levy, *et al.*, 1961)

DOSAGE FORM	MG APPARENT SALICYLATE EXCRETED IN URINE IN ONE HOUR: ARITHMETIC MEAN	GEOMETRIC MEAN	RANGE	AMOUNT OF ASPIRIN IN SOLUTION IN 10 MINS. IN VITRO[a]
C.T. ASA (Brand A)	12.5	11.5	4.23 to 17.1	257
C.T. ASA (Brand B)	14.6	12.5	3.98 to 28.3	313
Buffered tablets	17.2	15.8	6.11 to 28.4	411
ASA Solution	22.3	20.9	8.61 to 41.8	

[a] - Estimated from Figure 2 of Levy, *et al.* (1961)**

an empty stomach. The amounts of apparent salicylate excreted in the urine in one hour were determined in the same 12 subjects with each form. The three brands of aspirin tablets were tested *in vitro* in 0.1 N hydrochloric acid at 37°C. by the method of Levy and Hayes (1960). Results obtained by Levy, *et al.* (1961)** are given in Table 20.6.

(2) Equivalent doses of aspirin were administered, as less than 100 mesh powder (1.00 gram of aspirin and 1.12 gram aluminum acetylsalicylate), in random order to nine healthy male adults 30 to 60 minutes after the noon meal with exactly 100 ml of water. Urinary excretion of apparent salicylate was measured at 1 and 2 hours post administration. *In vitro* rates of dissolution from aspirin and aluminum acetylsalicylate 0.5 inch pellets, pressed at 50,000 p.s.i. and mounted in plexiglass holders, were determined in 200 ml of 0.1 N hydrochloric acid at 37°C in a 500 ml three-necked round-bottom flask using a rotational speed of 555 r.p.m. Data of Levy and Sahli (1962) are shown in Table 20.7.

Table 20.7. Amounts of Apparent Salicylate Excreted in the Urine of Nine Subjects at One and Two Hours Post Administration of Equivalent Oral Doses of 1 Gram of Aspirin and *in Vitro* Rates of Dissolution Determined by Rotating Pellet Method (Data of Levy and Sahli, 1962)

FORM ADMINISTERED	AVERAGE AMOUNTS OF APPARENT SALICYLATE (MG) EXCRETED IN THE URINE OF NINE SUBJECTS: 1 HOUR	2 HOURS	IN VITRO RATE OF DISSOLUTION MG/CM²/HR
Acetylsalicylic acid	14.7	50.9	65.1
Aluminum acetylsalicylate	5.23	19.7	8.88
Ratio: ASA / Al ASA	3.07	2.77	7.44

Spironolactone

The relationship of the absorption of spironolactone as reflected by the peak metabolite concentration in plasma of human subjects who ingested two different tablet forms of the drug was reported by Gantt *et al.* (1962).** These data are shown in Table 20.8. The correlation of these results with results of an *in vitro* rate of dissolution test was reported by Levy (1962). The *in vitro* data are reported in Table 20.9.

Table 20.8. Relationship Between Average Peak Metabolite Concentration in Human Plasma and Form of Spironolactone Administered (Data of Gantt *et al.* 1962)**

TABLET ADMINISTERED	DOSE (MG)	NO. OF SUBJECTS	AVERAGE PEAK METABOLITE CONCENTRATION IN PLASMA: µG/L	µG/L PER MG DRUG ADMINISTERED	RATIO
New tablet[a]	22.5	21	84.4	3.75	6.6
Original commercial tablet (Aldactone 100 mg)	100	24	56.5	0.57	

[a] - Apparently a similar or the same formulation as the new commercial tablet, Aldactone-A 25 mg, later sold by G. D. Searle & Co.

Table 20.9. *In Vitro* Rate of Dissolution Data[a] for the Original Commercial Tablet, Aldactone 100 mg (G. D. Searle & Co.) and the Replacement Product, Aldactone-A 25 mg (G. D. Searle & Co.)

TIME (MINS.)	PERCENT DISSOLVED: ALDACTONE 100 MG	PERCENT DISSOLVED: ALDACTONE-A 25 MG	RATIO OF % DISSOLVED: ALDACTONE-A/ ALDACTONE
5	0.43	18.1	42.1
10	1.08	28.1	26.0
15	2.61	33.6	12.9
20	4.24	37.6	8.9
25	5.70	40.8	7.2
30	7.0	43.2	6.2

[a] - Tabular data were supplied in personal communication by G. Levy and were published in graphical form by Levy (1962).

Prednisone

Campagna *et al.* (1963) reported a case history in which prednisone tablets meeting U.S.P. XVI specifications were substituted for a different brand name product and were found to be clinically ineffective. Both the clinically effective and clinically ineffective tablets passed the U.S.P. XVI tablet disintegration test. When the disintegration test was repeated without discs a large difference in disintegration time was noted between the two tablets. Both tablets were subjected to a dissolution test using the apparatus of Levy and Hayes (1960). The dissolution medium was 500 ml of water at 37°C. Results are shown in Table 20.10.

Table 20.10. Results of Disintegration and Dissolution Rate Tests on Clinically Active and Clinically Inactive Prednisone Tablets (from Campagna *et al.*, 1963)

PREDNISONE TABLETS	U.S.P. XVI DISINTEGRATION TIME (WITH DISCS) (MINS.)	DISINTEGRATION TIME (WITHOUT DISCS) (MINS.)	TIME FOR 50% OF DRUG TO DISSOLVE IN VITRO (MINS.): AVE.	TIME FOR 50% OF DRUG TO DISSOLVE IN VITRO (MINS.): S.D.[a]
Clinically active	<6	<6	4.3	1.3
Clinically inactive	<6	60-120	100	53

[a] - S.D.: Standard deviation

Table 20.11. *In Vivo* and *in Vitro* Rates of Dissolution of Methylprednisolone, Polymorphs I and II, in Pellet Form (from Hamlin *et al.*, 1962)

TEST	95% C.I. OF RATE OF DISSOLUTION (MG/CM²/HR): POLYMORPH I	95% C.I. OF RATE OF DISSOLUTION (MG/CM²/HR): POLYMORPH II	PERCENTAGE DIFFERENCE IN RATES[a]	SIGNIFICANCE OF DIFFERENCE BETWEEN RATES BY t-TEST
Pellet implant in rats	0.0179±0.0022	0.0302±0.0034	51.1	$p \leq .01$
Hanging pellet method *in vitro*	0.091±0.021	0.139±0.030	41.7	$p \leq .01$

[a] - Percentage difference in rates $= \frac{\text{Rate for polymorph II—Rate for polymorph I}}{\text{Average of rates for polymorphs I and II}} \times 100$

Methylprednisolone

Two polymorphic forms of methylprednisolone, designated polymorphs I and II, were studied both *in vivo* and *in vitro* by Hamlin *et al.* (1962). Pellets of the pure polymorphs, 0.25 inch in diameter, were compressed at high pressure. Two disks of one polymorph were implanted in each rat. After different intervals of time the pellets were removed and weighed. Knowing the loss in weight, the surface area and the time of exposure, the *in vivo* rate of dissolution (rate of weight loss, equivalent to the rate of absorption with opposite sign) was calculated. Thirty separate determinations involving three series of 10 different rats were used with polymorph I, and 15 separate determinations involving three series of five different rats were used with polymorph II. The average rates are shown in Table 20.11 but the complete data were published by Ballard and Nelson, (1962).

In the *in vitro* test pellets, 0.5 inch in diameter, were compressed at high pressure. The rates of dissolution in deionized water at 37°C were determined by the hanging pellet method of Nelson (1958). Data are shown in Table 20.11.

Ampicillin

The anhydrous and trihydrate forms of ampicillin were studied *in vivo* and *in vitro* by Poole *et al.*, (1968). Suspensions and capsules of both the anhydrous and trihydrate forms were administered at the 250 mg dose level to six dogs who were fasted overnight and dosed in crossover fashion for each dosage form studied. Blood samples were taken at 15, 30, 45, 60, 90, 120, 180 and 240 minutes post administration, and the sera were analyzed microbiologically for the antibiotic. In two crossover studies in human subjects, each employing 30 subjects, doses of 250 mg of the antibiotic were administered in the anhydrous or trihydrate forms—in one study as suspension and in the other study in capsules. Blood samples were taken at 0.5, 1, 2, 4 and 6 hours post administration and sera were analyzed as in the dog studies. Data are shown in Table 20.12.

The anhydrous form of ampicillin had slightly higher aqueous solubility and dissolved considerably more rapidly *in vitro* than the trihydrate form. *In vivo*, in both the dog and man, and in both suspension and capsule dosage forms, the anhydrous form of ampicillin gave somewhat higher areas under the serum concentration curve than the trihydrate form.

Griseofulvin

Griseofulvin plasma concentrations were measured at 2, 4, 8 and 25 hours after single 500 mg oral doses of four different griseofulvin preparations and at various times during seven days after 500 mg daily doses of three griseofulvin preparations in human subjects. Rates of dissolution of griseofulvin from the six different griseofulvin preparations were measured in simulated intestinal fluid over a 60-minute period (Symchowicz and Katchen, 1968). These authors showed that for both the single dose and multiple dose data taken separately there was an apparently linear correlation between the mean plasma level of griseofulvin and the logarithm of the milligrams of griseofulvin dissolved in 30 minutes in the *in vitro* test. It was noted by the present author that each set of percent-dissolved-time data reported by Symchowicz and Katchen (1968), gave a linear plot on logarithmic-probability graph paper; the times for 50 percent of griseofulvin to dissolve, $T_{50\%}$ (and the quantity $100/T_{50\%}$) were estimated graphically by this method and are shown in Table 20.13 along with the original authors' data.

Table 20.12. Areas Under Serum Concentration Curves in Dogs and Man and *in Vitro* $T_{50\%}$ Values for Ampicillin in Anhydrous and Trihydrate Forms (Data of Poole *et al.*, 1968)

	AREA (CM^2) UNDER SERUM CONCENTRATION CURVE				IN VITRO	
	DOG STUDIES		HUMAN STUDIES			AQUEOUS
FORM OF AMPICILLIN	SUSPENSION	CAPSULES	SUSPENSION	CAPSULES	$T_{50\%}$ (MINS.) FOR CAPSULES	SOLUBILITY AT 37° (MG/ML)
Anhydrous	152.5	100.2	143.5	127.8	7.5	10
Trihydrate	95.0	77.5	119.5	109.0	45	8

Table 20.13. Mean Plasma Levels After Single and Multiple Doses of 500 mg of Griseofulvin Administered to Human Subjects in Six Different Preparations and Correlation with *in Vitro* Dissolution Rate Results

	MEAN PLASMA LEVEL (μG/ML) IN MAN		IN VITRO DATA		
GRISEOFULVIN PREPARATION	SINGLE DOSE	MULTIPLE DOSE	MG DISSOLVED IN 30 MINS.[a]	$T_{50\%}$ (MINS.)	$100/T_{50\%}$
1	1.02	–	97	8.5	11.8
5	–	1.65	94	9.5	10.5
4	0.93	–	55	21.8	4.58
2	0.83	1.50	50	28.5	3.51
3	0.74	–	35	55.0	1.82
6	–	1.42	33	81.0	1.23

[a] - Data of Symchowicz and Katchen (1968).
[b] - Estimated by J. G. Wagner from linear logarithmic-probability plot of percent dissolved (on probability axis) versus time (on logarithmic axis).

The mean plasma levels of griseofulvin, for the single dose and multiple dose studies taken separately, are rank-order correlated with both the amount of griseofulvin dissolved *in vitro* in 30 minutes and with the reciprocals of the time for 50 percent of the griseofulvin to dissolve ($100/T_{50\%}$).

Sulfamethazine

Taraszka and Delor (1969) studied the effect of rate of dissolution of sulfamethazine from tablets on the absorption and excretion of the drug. Fast, medium and slowly-dissolving tablets were studied in man and in *in vitro*. Some of their results are summarized in Table 20.14.

Table 20.14. Comparison of Average Areas under the Total Concentration Curves in Man and the Times for 50 Percent of the Drug to Dissolve *in Vitro* for three Sulfamethazine Tablets (Data of Taraszka and Delor, 1969)

TYPE OF TABLET	AREA UNDER TOTAL CONCENTRATION CURVE IN MAN (MG% X HR)	SIGNIFICANCE LEVEL OF DIFFERENCE	IN VITRO $T_{50\%}$ (MINS.)
Fast	129.2		3.9
		$p \leq .05$	
Medium	127.2		16.7
		$p \leq .05$	
Slow	116.8		46.7

Salicylamide

Four healthy volunteers ingested 0.6 Gm salicylamide as an aqueous solution (250 ml), a commercial suspension, two 0.3 Gm commercial tablets and two 0.3 Gm experimental tablets at different times. The subjects were fasted overnight and for two hours post dosing. Urine was collected at hourly intervals for the first eight hours and for a total of 36 hours post drug ingestion. Total salicylamide in the urine was determined colorimetrically. *In vitro* rates of dissolution were determined in 0.1 N HCl by a flask-stirrer method at 70 r.p.m. The human data of Bates, *et al.*, (1969)[••] are summarized in Table 20.15 and the *in vitro* data are summarized in Table 20.16.

Table 20.15. Effect of Dosage Form on the Cumulative Amount Excreted in One Hour and Relative Physiological Availability of Salicylamide (from Bates, *et al.*, 1969)**

DOSAGE FORM	PERCENTAGE OF 0.6 GM DOSE EXCRETED IN URINE IN ONE HOUR		PHYSIOLOGICAL AVAILABILITY BASED ON 36-HOUR EXCRETION (PERCENT)
	AVE.	RANGE	
Aqueous solution	35.1	29.8-43.0	100.0
Commercial suspension	22.8	16.9-26.1	97.3
Commercial tablet	7.1	4.9-9.6	91.5
Experimental tablet	2.0	1.7-2.7	55.5

Table 20.16. Initial Dissolution Rates of Salicylamide Preparations in 0.1 N HCl at 37°C (from Bates, *et al.*, 1969)**

TIME (MIN.)	PERCENT SALICYLAMIDE DISSOLVED		
	COMMERCIAL SUSPENSION	COMMERCIAL TABLET	EXPERIMENTAL TABLET
2	21.0	–	0.7
5	31.0	1.4	2.2
10	41.6	6.8	3.7
15	48.4	13.6	5.1
20	55.8	22.3	6.8
25	61.7	35.2	8.0
30	67.2	44.9	9.6

In these studies the experimental tablet was prepared by slugging the salicylamide with 1 percent magnesium stearate as lubricant. For suspension and two tablet dosage forms the authors reported linear correlations between the percent of the dose excreted at one hour and the percent in solution *in vitro* in 15 minutes and in 20 minutes.

Summary

Twelve rank order correlations of *in vivo* data with *in vitro* rate of dissolution data, involving ten different drugs, have been summarized in this section. A variety of *in vivo* parameters are employed in the correlations. Many different types of *in vitro* tests were employed to obtain the *in vitro* parameters. Hence the correlations are quite specific to the experimental conditions employed by the various authors. However, it may be inferred that the differences measured *in vitro* in large part explain the differences in the parameters measured *in vivo*.

References

1. MacDonald, H., Pisano, F., Burger, J., Dornbush, A. and Pelcak, E.: Physiological Availability of Various Tetracyclines, *Drug Information Bull. 3*:76-81 (1) 1969.

2. Levy, G., Gumtow, R. H. and Rutowski, J. M.: The Effect of Dosage Form Upon the Gastrointestinal Absorption Rate of Salicylates, *Can. Med. Assoc. J. 85*:414-419, 1961.

3. Gantt, C. L., Gochman, N. and Dyniewicz, J. M.: Gastrointestinal Absorption of Spironolactone, *Lancet* May 26, p. 1130-1131, 1962.

4. Bates, T. R., Lambert, D. A. and Johns, W. H.: Correlation Between the Rate of Dissolution and Absorption of Salicylamide from Tablet and Suspension Dosage Forms, *J. Pharm. Sci. 58*:1468-1470, 1969.

Rate of Dissolution Chronological Bibliography

Chronological Bibliography on Rate of Dissolution In Vitro and In Vivo and Related References

1. Noyes, A. A. and Whitney, W. R.: The Rate of Solution of Solid Substances in Their Own Solutions, *J. Am. Chem. Soc. 19*:930-934, 1897.

2. Bruner, L. and Tolloczko, St.: Über die Auflösungsgeschwindigkeit fester Körper, *Zeit. Phys. Chem. 35*:283-290, 1900.

3. Bruner, L. and Tolloczko, St.: Über die Auflösungsgeschwindigkeit fester Körper, *Zeit. Anorg. Chem. 28*:314-330, 1901.

4. Hance, A. M.: Solubility of Compressed Tablets, *Am. J. Pharm. 74*:80-83, 1902.

5. Bruner, L. and Tolloczko, St.: Über die Auflösungsgeschwindigkeit fester Körper, *Zeit. Anorg. Chem. 35*:23-40, 1903.

6. Nernst, W. and Brunner, E.: Theorie der Reakstionsgeschwindigkeit in heterogenen Systemen. Reaktionsgeschwindigkeit in heterogen Systemen, *Zeit. Phys. Chem. 47*:52-55, 56-102, 1904.

7. Bruner, M. L. and Tolloczko, St.: Über die Auflösungsgeschwindigkeit fester Körper, *Zeit Anorg. Chem. 56*: 58-71, 1907.

8. Wilderman, M.: Über die Geschwindigkeit molecularer und chemisches Reactionen in heterogenen Systemen, *Zeit Phys. Chem. 66*:445-495, 1909.

9. Lewis, W. K.: The Principles of Counter-Current Extraction, *Ind. Eng. Chem. 8*:825-833, 1916.

10. Hixson, A. W. and Crowell, J. H.: Dependence of Reaction Velocity Upon Surface and Agitation. I. Theoretical Consideration, *Ind. Eng. Chem. 23*:923-931, 1931; *ibid.* II. Experimental Procedure in Study of Surface, *ibid. 23*: 1002-1009, 1931.

11. Klein, I.: *Bull. Biologietes Pharmaciens 1932*, p. 273.

12. Elliott, G. H.: The Rate of Solution of Tablets. A Method for Its Determination, *Pharm. J. 131*:514, 1933.

13. King, C. V. and Brodie, S. S.: The Rate of Dissolution of Benzoic Acid in Dilute Aqueous Alkali, *J. Am. Chem. Soc. 59*:1375-1379, 1937.

14. Marshall, E. K., Jr., Cutting, W. C. and Emerson, K.: The Toxicity of Sulfanilamide, *J. Am. Med. Assoc. 110*: 252-257, 1938.

15. Marshall, E. K., Jr., Brattan, A. C. and Litchfield, J. R.: The Toxicity and Absorption of 2-Sulfanilamidopyridine and Its Soluble Sodium Salt, *Science 88*:597-599, 1938.

16. Barlow, O. W. and Clemenko, D. R.: Studies on the Pharmacology of Sulfapyridine and Sulfathiazole; Absorption of the Free Acid, the Sodium Salt and the Glucoside from the Alimentary Tract, *J. Am. Med. Assoc. 116*:282-286, 1941.

17. Lark-Horowitz, K. and Leng, H. R.: Radioactive Indicators, Enteric Coatings and Intestinal Absorption, *Nature 147*:580-581, 1941.

18. Hixson, A. W. and Baum, S. J.: Mass Transfer and Chemical Reaction in Liquid-Solid Agitation, *Ind. Eng. Chem. 36*:528-531, 1944.

19. Melnick, D., Hochberg, M. and Oser, B. L.: Physiological Availability of the Vitamins, *J. Nutrition 30*:67-79, 1945.

20. Oser, B. L., Melnick, D. and Hochberg, M.: Physi-

ological Availability of the Vitamins. Study of Methods for Determining Availability in Pharmaceutical Products, *Ind. Eng. Chem. Anal. Ed. 17*:401-411, 1945.

21. Zdanovski, A. B.: Rate of Solution of Sodium Chloride and Potassium Chloride Crystals, *J. Phys. Chem. (U.S.S.R.) 20*:379-386, 1946.

22. Snapper, I., Greenspan, E. and Saltzman, A.: Differences in Excretion of Hippuric Acid and Glucuronate After Ingestion of Sodium Benzoate and Benzoic Acid, *Am. J. Digest. Diseases 13*:275-278, 1946.

23. Wagner, C.: The Dissolution Rate of Sodium Chloride with Diffusion and Natural Convection as Rate-Limiting Factors, *J. Phys. Chem. 53*:1030-1033, 1949.

24. Truitt, E. B., Jr., McKusick, V. A. and Krantz, J. C., Jr.: Theophylline Blood Levels After Oral, Rectal and Intravenous Administration and Correlation with Diuretic Action, *J. Pharmacol. Exptl. Therap. 100*:309-315, 1950.

25. Danckwerts, P. V.: Significance of Liquid-Film Coefficients in Gas Absorption, *Ind. Eng. Chem. 43*:1460-1467, 1951.

26. Smith, M. J. H.: Plasma Salicylate Concentrations After Small Doses of Acetylsalicylic Acid, *J. Pharm. Pharmacol. 3*:409-413, 1951.

27. Edwards, L. J.: The Dissolution and Diffusion of Aspirin in Aqueous Media, *Trans. Faraday Soc. 47*:1191-1210, 1951.

28. Jost, W.: "Diffusion in Solids, Liquids, Gases," Academic Press, Inc., New York, N. Y., 1952, p. 78.

29. Bircumschaw, M. A. and Riddiford, A. C.: Transport Control in Heterogeneous Reactions, *Chem. Soc. Quart. Rev. (London) 6*:157-185, 1952.

30. Davion, M.: Étude sur la Vitesse de Dissolution des Sels Crystallisés, Thesis 370, University of Paris, France, 1953.

31. Piney, A.: Prolonging the Effects of Drugs Administered by Mouth, *Brit. Med. J. 2*:48-49, 1954.

32. Josselyn, L. E., Endicott, C. and Sylvester, J. C.: Absorption of Erythromycin III. Various Pharmaceutical Factors, *Antibiotics Annual 1954-55*, p. 279-282.

33. Parrott, E. L., Wurster, D. E. and Higuchi, T.: Investigation of Drug Release From Solids I. Some Factors Influencing the Dissolution Rate, *J. Am. Pharm. Assoc. Sci. Ed. 44*:269-273, 1955.

34. Putman, L. E., Wright, W. W., De Nunzio, A. and Welch, H.: Penicillin Blood Concentrations Following Oral Administration of Various Dosage Forms of Penicillin V and Comparison with Penicillin G, *Antibiotics Annual 1955-56*, p. 483-489.

35. Cohen, R. V., Malthan, L. and Zarafonetis, J. D.: Clinical Studies of Various Forms of PAS, *Diseases Chest 30*:1-11, 1956.

36. Kaipainen, W. J. and Harkonen, P.: Serum Concentrations After Oral Administration of Phenoxymethylpenicillin Acid and Phenoxymethylpenicillin Potassium, *J. Lab. Clin. Invest. 8*:18-20, 1956.

37. Johnson, A. I. and Huang, C. J.: Mass Transfer Studies in an Agitated Vessel, *A. I. Ch. E. J. 2*:412-419, 1956.

38. Gregory, D. P. and Riddiford, A. C.: Transport to the Surface of a Rotating Disk, *J. Chem. Soc. (London)*, p. 3756-3764, 1956.

39. Nelson, E.: Solution Rate of Theophylline Salts and Effects from Oral Administration, *J. Am. Pharm. Assoc. Sci. Ed. 46*:607-614, 1957.

40. Schulger, J., McGinn, J. T. and Hennesey, D.: Comparative Theophylline Blood Levels Following Oral Administration of Three Different Theophylline Preparations, *Am. J. Med. Sci. 233*:296-302, 1957.

41. Colquhoun, J., Scorer, E. C., Sandler, G. and Wilson, G. M.: Absorption of Free Acid, Potasium and Benzathine Phenoxymethylpenicillin After Oral Administration, *Brit. Med. J. 1*:1451-1452, 1957.

42. Brodie, B. B. and Hogben, C. A. M.: Some Physico-Chemical Factors in Drug Action, *J. Pharm. Pharmacol. 9*: 345-380, 1957.

43. Nelson, E.: Comparative Dissolution Rates of Weak Acids and Their Sodium Salts, *J. Am. Pharm. Assoc. Sci. Ed. 47*:297-299, 1958a.

44. Nelson, E.: Dissolution Rate of Mixtures of Weak Acids and Tribasic Sodium Phosphate, *J. Am. Pharm. Assoc. Sci. Ed. 47*:300-302, 1958b.

45. Higuchi, W. I., Parrott, E. L., Wurster, D. E. and Higuchi, T.: Investigation of Drug Release from Solids II. Theoretical and Experimental Study of Influences of Bases and Buffers on Rates of Dissolution of Acidic Solids, *J. Am. Pharm. Assoc. Sci. Ed. 47*:376-383, 1958.

46. Blubaugh, F. C., Zapapas, J. R. and Sparks, M. C.: An Enteric Compression Coating I. *In Vitro* Studies, *J. Am. Pharm. Assoc. Sci. Ed. 47*:857-862, 1958.

47. Robinson, M. J., Bondi, A., Jr. and Swintosky, J. V.: Sulfamethylthiadiazole: Human Blood Concentrations and Urinary Excretion Data Following Oral Doses, *J. Am. Pharm. Assoc. Sci. Ed. 47*:874-878, 1958.

48. Furész, J.: Blood Levels Following Oral Administration of Different Preparations of Novobiocin, *Antibiot. Chemotherapy 8*:446-450, 1958.

49. Gottfried, P. M.: 1,3-Dichloro-5,5-Dimethyl Hydantoin Compositions, U. S. patent 2,863,800, December 9. 1958.

50. Souder, J. C. and Ellenbogen, W. C.: Laboratory Control of Dextro-Amphetamine Sulfate Sustained Release Capsules, *Drug Std. 26*:77-83, 1958.

51. Nelson, E.: Influence of Dissolution Rate and Surface on Tetracycline Absorption, *J. Am. Pharm. Assoc. Sci. Ed. 48*:96-103, 1959.

52. Nelson, E. and Schaldemose, I.: Urinary Excretion Kinetics for Evaluation of Drug Absorption I. Solution Rate Limited and Nonsolution Rate Limited Absorption of Aspirin and Benzylpenicillin; Absorption Rate of Sulfaethylthiadiazole, *J. Am. Pharm. Assoc. Sci. Ed. 48*:489-495, 1959.

53. Royal, J.: A Comparison of *in Vitro* Rates of Release of Several Brands of Dextro Amphetamine Sulfate Sustained Release Capsules, *Drug Std. 27*:1-6, 1959.

54. Shenoy, K. G., Chapman, D. G. and Campbell, J. A.: Sustained Release in Pelleted Preparations as Judged by Urinary Excretion and *in Vitro* Methods, *Drug Std. 27*:77-84, 1959.

55. Vliet, E. B.: A Suggested *in Vitro* Procedure for Measuring the Rate of Release from Timed Release Tablets and Capsules, *Drug Std. 27*:97-99, 1959.

56. Wiegand, R. G. and Taylor, J. D.: An Exponential Expression for *in Vitro* Release of Drug from Sustained Release Preparations, *Drug Std. 27*:161-171, 1959 and *ibid. 28*:31-32, 1960.

57. Wagner, J. G.: Sustained Action Oral Medication II. The Kinetics of Release of Drugs to Fluids *in Vitro, Drug Std. 27*:178-186, 1959; *ibid. 28*:30, 1960.

58. Holundahlson, K. H. and Lodin, H.: Absorption of Iopanoic Acid and Its Sodium Salt, *Acta Radiol. 51*:247-250, 1959.

59. Nelson, E. Urinary Excretion Kinetics for Evaluation of Drug Absorption II. Constant, Rate-Limited Release of Tetracycline After Ingestion in Humans, *J. Am. Pharm. Assoc. Sci. Ed. 49*:54-56, 1960.

60. Wurster, D. E. and Seitz, J. A.: Investigation of Drug Release from Solids III. Effect of Changing Surface-Weight Ratio on the Dissolution Rate, *J. Am. Pharm. Assoc. Sci. Ed. 49*:335-338, 1960.

61. Nelson, E.: Urinary Excretion Kinetics for Evaluation of Drug Absorption III. Method for Calculation of Absorption Rate and Application to Tetracycline Absorption in Humans, *J. Am. Pharm. Assoc. Sci. Ed. 49*:437-440, 1960.

62. Nash, R. A. and Marcus, A. D.: An *in Vitro* Method for the Evaluation of Sustained Release Products, *Drug Std. 28*:1-5, 1960.

63. Vliet, E. B.: Progress Report on Studies to Develop an *in Vitro* Procedure for Measuring the Rate of Drug Release Tablets and Capsules, *Drug Std. 28*:113-114, 1960.

64. Losinski, E.: Physiological Availability of Dicoumarol, *Can. Med. Assoc. J. 83*:177-178, 1960.

65. Levy, G. and Hayes, B. A.: Physiochemical Basis

of the Buffered Acetylsalicylic Acid Controversy, *New Engl. J. Med. 262*:1053-1058, 1960.

66. Wagner, J. G., Carpenter, O. S. and Collins, E. J.: Sustained Action Oral Medication I. A Quantitative Study of Prednisolone in Man, in the Dog and *in Vitro*, *J. Pharmacol. Exptl. Therap. 129*:101-107, 1960.

67. Sjögren, J.: Laboratory Control of Duretter, A Sustained Release Tablet, *Dansk. Tidsskr. Farm. 34*:189-201, 1960.

68. Schneider, A. E. and Joen K.: Investigation on the Dissolution Rate of Sucrose in Electrolyte Containing Solutions, *Zucker-Beih. 4*:1-11, 1960, Part I.

69. Campbell, J. A. Evaluation of Sustained-Action Release Rates, *Drug Cosmetic Ind. 87*:620, 1960.

70. Stone, I. M. (Assigner to Baxter-Laboratories, Inc.): Water Dispensible Antibiotics, U. S. Patent 3,089,818 (Filed June 2, 1960).

71. Wagner, J. G.: Biopharmaceutics: Absorption Aspects, *J. Pharm. Sci. 50*:359-387, 1961.

72. Levy, G.: Comparison of Dissolution and Absorption Rates of Different Commercial Aspirin Tablets, *J. Pharm. Sci. 50*:388-392, 1961.

73. O'Reilly, I. and Nelson, E.: Urinary Excretion Kinetics for Evaluation of Drug Absorption IV. Studies with Tetracycline Absorption Enhancement Factors, *J. Pharm. Sci. 50*:413-416, 1961.

74. Higuchi, T.: The Role of Crystal Structure on Availability and Stability of Some Pharmaceuticals, Teachers' Seminar on Pharmacy, 1961.

75. Sekiguchi, K. and Obi, N.: Studies on Absorption of Eutectic Mixture I. A. Comparison of the Behavior of Eutectic Mixture of Sulfathiazole and That of Ordinary Sulfathiazole in Man, *Chem. Pharm. Bull. (Tokyo) 9*:866-872, 1961.

76. Myullery, R. L., Berisova, Z. U. and Grebenshchikou: The Kinetics of Arsenic Selenide Dissolution in Alkaline Solution, *J. Appl. Chem. (USSR) 34*:513-517, 1961.

77. Kapmer, R. S. and Hoelscher, H. E.: Kinetics and Mechanism of Zinc Dissolution in Acid, *Ind. Eng. Chem. 53*:239-244, 1961.

78. Levy, G. and Sahli, B. A.: Comparison of the Gastrointestinal Absorption of Aluminum Acetylsalicylate and Acetylsalicylic Acid in Man, *J. Pharm. Sci. 51*:58-62, 1962.

79. Krueger, E. O. and Vliet, E. B.: *In Vitro* Testing of Timed Release Tablets and Capsules, *J. Pharm. Sci. 51*:181-184, 1962.

80. Levy, G. and Procknall, J. A.: Unusual Dissolution Behavior Due to Film Formation, *J. Pharm. Sci. 51*:294, 1962.

81. Hamlin, W. E., Nelson, E., Ballard, B. E. and Wagner, J. G.: Loss of Sensitivity in Distinguishing Real Differences in Dissolution Rates Due to Increasing Intensity of Agitation, *J. Pharm. Sci. 51*:432-435, 1962.

82. Nelson, E., Knoechel, E. L., Hamlin, W. E. and Wagner, J. G.: Influence of the Absorption Rate of Tolbutamide on the Rate of Decline of Blood Sugar Levels in Normal Humans, *J. Pharm. Sci. 51*:509-514, 1962.

83. Schroeter, L. C., Tingstad, J. E., Knoechel, E. L. and Wagner, J. G.: The Specificity of the Relationship Between Rate of Dissolution and Disintegration Time of Compressed Tablets, *J. Pharm. Sci. 51*:865-874, 1962.

84. Ballard, B. E. and Nelson, E.: Absorption of Implanted Solid Drug, *J. Pharm. Sci. 51*:915-924, 1962.

85. Schroeter, L. C. and Wagner, J. G.: Automated Dissolution Rate Studies of Capsules and Tablets, *J. Pharm. Sci. 51*:957-962, 1962.

86. Morozowich, W., Chulski, T., Hamlin, W. E., Jones, P. M., Northam, J. I., Purmalis, A. and Wagner, J. G.: Relationship Between *in Vitro* Dissolution Rates, Solubilities and LT_{50}'s in Mice of Some Salts of Benzphetamine and Etryptamine, *J. Pharm. Sci. 51*:993-996, 1962.

87. Levich, V. G.: "Physiochemical Hydrodynamics," Prentice-Hall, Inc., Englewood Cliffs, N. J., 1962.

88. Levy, G.: Availability of Spironolactone Given by Mouth, *Lancet* October 6, 1962, p. 723-724.

89. Cooper, A. R., Jr. and Kingery, W.: Kinetics of Solution in High Viscosity Liquids: Sodium Chloride-Glycerol, *J. Phys. Chem. 66*:665-669, 1962.

90. Ballard, B. E. and Nelson, E.: Physicochemical Properties of Drugs that Control Absorption Rate After Subcutaneous Implantation, *J. Pharmacol. Exptl. Therap. 135*:120-127, 1962.

91. Nelson, E.: Physiochemical Factors Influencing the Absorption of Erythromycin and Its Esters, *Chem. Pharm. Bull. (Tokyo) 10*:1099-1101, 1962.

92. Bauer, G., Rieckmann, P. and Schaumann, W.: Einfluss von Teilchengrösse und Lösungsvermittlern auf der Resorption von Spironolacton aus dem Magen-Darmtrakt, *Arzneimittel-Forsch. 12*:487-489, 1962.

93. Bergman, I., Cartwright, J. and Bentley, R. A.: A Mechanism for the Dissolution of Ground Quartz Powder in Dilute Hydrofluoric Acid, An 'Easily Soluble Core' and Its Relation to the 'Easily Soluble Layer,' *Nature 196*:248-250, 1962.

94. Bergman, I.: Silica Powders of Respirable Size II. Dissolution Rates in Dilute Hydrofluoric Acid. *J. Appl. Chem. 12*:336, 1962.

95. Kawashi, K.: On the Variation of Wettability of Organic Solids in Contact with Water, *J. Colloid Sci. 17*: 169-177, 1962.

96. Niebergall, P. J. and Goyan, J. E.: Dissolution Rate Studies I. Continuous Recording Technique for Following Rapid Reactions in Solution, *J. Pharm. Sci. 52*:29-33, 1963a.

97. Higuchi, W. I. and Hiestand, E. N.: Dissolution Rates of Finely Divided Drug Powders I. Effect of Distribution of Particle Size in a Diffusion-Controlled Process, *J. Pharm. Sci. 52*:67-71, 1963.

98. Higuchi, W. I., Lau, P. K., Higuchi, T. and Shell, J. W.: Polymorphism and Drug Availability. Solubility Relationships in the Methylprednisolone System, *J. Pharm. Sci. 52*:150-153, 1963.

99. Higuchi, W. I., Rowe, E. L. and Hiestand, E. N.: Dissolution Rates of Finely Divided Drug Powders II. Micronized Methylprednisolone, *J. Pharm. Sci. 52*:162-164, 1963.

100. Niebergall, P. J., Milosovich, G. and Goyan, J. E.: Dissolution Rate Studies II. Dissolution of Particles Under Conditions of Rapid Agitation, *J. Pharm. Sci. 52*:236-241, 1963b.

101. Ballard, B. E. and Nelson, E.: Absorption and Excretion of Sulfadiazine After Subcutaneous Implantation of Disks in Rats, *J. Pharm. Sci. 52*:301-303, 1963.

102. Higuchi, W. I. and Hamlin, W. E.: Release of Drug from a Self-Coating Surface. Benzphetamine Pamoate Pellet, *J. Pharm. Sci. 52*:575-579, 1963.

103. Campagna, F. A., Cureton, G., Merigian, R. A. and Nelson, E.: Inactive Prednisone Tablets U.S.P. XVI, *J. Pharm. Sci. 52*:605-606, 1963.

104. Levy, G. and Gagliardi, B. A.: Gastrointestinal Absorption of Aspirin Anhydride, *J. Pharm. Sci. 52*:730-732, 1963.

105. Shefter, E. and Higuchi, T.: Dissolution Behavior of Crystalline Solvated and Nonsolvated Forms of Some Pharmaceuticals, *J. Pharm. Sci. 52*:781-791, 1963.

106. Schroeter, L. C. and Hamlin, W. E.: Modified Automated Apparatus for Determination of Dissolution Rates of Capsules and Tablets, *J. Pharm. Sci. 52*:811-813, 1963.

107. Levy, G., Antkowiak, J. M., Procknall, J. A. and White, D. C.: Effect of Certain Tablet Formulation Factors on Dissolution Rate of the Active Ingredient II. Granule Size, Starch Concentration, and Compression Pressure, *J. Pharm. Sci. 52*:1047-1051, 1963.

108. Levy, G.: Effect of Certain Tablet Formulation Factors on Dissolution Rate of the Active Ingredient I. Importance of Using Appropriate Agitation Intensities for *in Vitro* Dissolution Rate Measurements to Reflect *in Vivo* Conditions, *J. Pharm. Sci. 52*:1039-1046, 1963.

109. Levy, G. and Gumtow, R. H.: Effect of Certain Tablet Formulation Factors on Dissolution Rate of the Active

Ingredient III. Tablet Lubricants, *J. Pharm. Sci. 52*:1139-1144, 1963.

110. Higuchi, T.: Mechanism of Sustained-Action Medication. Theoretical Analysis of Rate of Release of Solid Drugs Dispersed in Solid Matrices, *J. Pharm. Sci. 52*:1145-1149. 1963.

11. Macek, T. J.: Influence of Product Formulation on Therapeutic Activity, *Minnesota Pharmacist 18*:17-18, 1963; *ibid. 18*:22, 27, 30, 1963.

112. Gwilt, J. R., Robertson, A., Goldman, L. and Blanchard, A. W.: The Absorption Characteristics of Paracetamol Tablets in Man, *J. Pharm. Pharmacol. 15*:445-453, 1963.

113. Leonards, J. R.: The Influence of Solubility on the Rate of Gastrointestinal Absorption of Aspirin, *Clin. Pharmacol. Therap. 4*:476-479, 1963.

114. Wagner, J. G.: "The Case for *in Vitro* Rate of Dissolution as a Criterion for *in Vivo* Rate of Absorption and for Availability of Drug for Absorption," presented at the Fifth Annual National Pharmaceutical Research Conference, Land O'Lakes, Wisconsin, June 16-20, 1963.

115. Wagner, J. G.: "Pharmaceutics of Drug Absorption—Case Histories. Part I. Orinase," presented at the Fifth Annual National Pharmaceutical Research Conference, Land O'Lakes, Wisconsin, June 16-20, 1963.

116. Kanig, J. L.: Properties of Fused Mannitol in Compressed Tablets, *J. Pharm. Sci. 53*:188-192, 1964.

117. Higuchi, W. I., Nelson, E. and Wagner, J. G.: Solubility and Dissolution Rates in Reactive Media, *J. Pharm. Sci. 53*:333-335, 1964.

118. Montgomery, K. D., Flemming, C. V., Weinswig, M. H., Parke, R. F. and Swartz, H. A.: *In Vitro* Evaluation of Sustained-Release Tablets by Dual Channel Scintillation Counting, *J. Pharm. Sci. 53*:340-341, 1964.

119. Ballard, B. E., Ballard, S. S. and Nelson, E.: Effect of Temperature on Absorption Rate of Drug Implants, *J. Pharm. Sci. 53*:424-428, 1964.

120. Vora, M. S., Zimmer, A. J. and Maney, P. V.: Sustained-Release Aspirin Tablet Using an Insoluble Matrix, *J. Pharm. Sci. 53*:487-492, 1964.

121. Levy, G. and Procknall, J. A.: Dissolution Rate Studies on Methylprednisolone Polymorphs, *J. Pharm. Sci. 53*:656-658, 1964.

122. Levy, G. and Tanski, W., Jr.: Precision Apparatus for Dissolution Rate Determinations, *J. Pharm. Sci. 53*:679, 1964.

123. Lazarus, J., Pagliery, M. and Lachman, L.: Factors Influencing the Release of a Drug from a Prolonged-Action Matrix, *J. Pharm. Sci. 53*:798-802, 1964.

124. Wood, J. H. and Syarto, J.: Wurster Coated Aspirin II. An *in Vitro* and *in Vivo* Correlation of Rate from Sustained-Release Preparations, *J. Pharm. Sci. 53*:877-881, 1964.

125. Nelson, E., Long, S. and Wagner, J. G.: Correlation of Amount of Metabolite Excreted and Its Excretion Rate with Available Surface Area of Tolbutamide in Dosage Form, *J. Pharm. Sci. 53*:1224-1227, 1964.

126. Wagner, J. G. and Nelson, E.: The Kinetic Analysis of Blood Levels and Urinary Excretion in the Absorptive Phase After Single Doses of Drug, *J. Pharm. Sci. 53*:1392-1403, 1964.

127. Lieberman, S. V. and Wood, J. H.: Aspirin Formulation and Absorption Rate II. Influence on Serum Levels of Tablets, Antacids and Solutions, *J. Pharm. Sci. 53*:1492-1495, 1964.

128. Marcus, A. D.: "Of What Value Are Dissolution Rates?" presented at a Regional Meeting of the Industrial Pharmacy Section, APhA, Chicago, Illinois, November 13, 1964.

129. Levy, G.: Effect of Dosage Form Properties on Therapeutic Efficacy of Tolbutamide Tablets, *Can. Med. Assoc. J. 90*:978-979, 1964.

130. Kokowski, C. J.: Pharmaceutical Basis of the Knowledge of Drugs, *Am. J. Hosp. Pharm. 21*:112-117, 1964.

131. Sekiguchi, K., Obi, N. and Ueda, Y.: Studies on Absorption of Eutectic Mixture II. Absorption of Fused Conglomerates of Chloramphenicol and Urea in Rabbits, *Chem. Pharm. Bull. (Tokyo) 12*:134-144, 1964.

132. Yen, J. K. C.: The Dissolution Rate Principle in Practical Tablet Formulation, *Can. Pharm. J. Sci. Sect. 97*: 25-31, 1964.

133. Ballard, B. E. and Biles, J. A.: Effect of Crystallizing Solvent on Absorption Rate of Steroid Implants, *Steroids 4*: 273-278, 1964.

134. Anderson, K. W.: The Oral Absorption of Quinalbarbitone and Its Sodium Salt, *Arch. Intern. Pharmacodyn. 147*:171-177, 1964.

135. Contacas, P. G., Coatney, G. R., Lunn, J. S. and Kilpatrick, J. W.: The Antimalarial Activity of CI-501 (Camolar) Against Falciparum Malaria, *Am. J. Trop. Med. Hyg. 13*:386-390, 1964.

136. Sevelius, H. and Colmore, J. P.: Experimental Design for Evaluation of Non-Narcotic Analgesic Agents. A Comparison of Aspirin, Buffered Aspirin, Sustained-Release Salicylate and Placebo, *J. New Drugs 4*:337-346, 1964.

137. Rashkovich, L. H. and Menkovskaya, E. M.: Determination of Solubility and Diffusion Coefficients from Kinetic Data, *Kolloidn. Zh. 26*:485, 1964.

138. Higuchi, W. I., Mir, N. A., Parker, A. P. and Hamlin, W. E.: Dissolution Kinetics of a Weak Acid, 1,1-Hexamethylene p-Tolylsulfonyl-Semicarbazide, and Its Sodium Salt, *J. Pharm. Sci. 54*:8-11, 1965.

139. Higuchi, W. I. and Saad, H. Y.: Cholesterol Particle Growth and Dissolution Rates in Aqueous Media, *J. Pharm. Sci. 54*:74-78, 1965.

140. Wurster, D. E. and Taylor, P. W.: Dissolution Rates, *J. Pharm. Sci. 54*:169-175, 1965.

141. Goyan, J. E.: Dissolution Rate Studies III. Penetration Model for Describing Dissolution of a Multicompartment System, *J. Pharm. Sci. 54*:645-647, 1965.

142. Wurster, D. E. and Taylor, P. W., Jr.: Dissolution Kinetics of Certain Crystalline Forms of Prednisolone, *J. Pharm. Sci. 54*:670-676, 1965.

143. Wood, J. H., Syarto, J. E. and Letterman, H.: Improved Holder for Intrinsic Dissolution Rate Studies, *J. Pharm. Sci. 54*:1068, 1965.

144. Levy, G. and Hollister, L. E.: Dissolution Rate-Limited Absorption in Man. Factors Influencing Drug Absorption from Prolonged-Release Dosage Form, *J. Pharm. Sci. 54*:1121-1125, 1965.

145. Goldberg, A. H., Gibaldi, M. and Kanig, J. L.: Increasing Dissolution Rates and Gastrointestinal Absorption of Drugs *via* Solid Solutions and Eutectic Mixtures I. Theoretical Considerations and Discussion of the Literature; *J. Pharm. Sci. 54*:1145-1148, 1965.

146. Wood, J. H.: *In Vivo* Drug Release Rate from Hard Gelatin Capsules, *J. Pharm. Sci. 54*:1207-1208, 1965.

147. Calesnick, B., Katchen, B. and Black, J.: Importance of Dissolution Rates in Producing Effective Diazotide Blood Levels in Man, *J. Pharm. Sci. 54*:1277-1280, 1965.

148. Saad, H. Y. and Higuchi, W. I.: Cholesterol Particle Growth and Dissolution Rates II. Retardation Effects of Cholate, *J. Pharm. Sci. 54*:1303-1307, 1965.

149. Higuchi, W. I., Mir, N. A. and Desai, S. J.: Dissolution Rates of Polyphase Mixtures, *J. Pharm. Sci. 54*:1405-1410, 1965.

150. Stelmach, H., Robinson, J. R. and Erikson, S. P.: Release of Drug from a Dosage Form, *J. Pharm. Sci. 54*: 1453-1458, 1965.

151. Desai, S. J., Simonelli, A. P. and Higuchi, W. I.: Investigation of Factors Influencing Release of Solid Drugs Dispersed in Inert Matrices, *J. Pharm. Sci. 54*:1459-1464, 1965.

152. Hamlin, W. E., Northam, J. I. and Wagner, J. G.: Relationship Between *in Vitro* Dissolution Rates and Solubilities of Numerous Compounds Representative of Various Chemical Species, *J. Pharm. Sci. 54*:1651-1653, 1965.

153. Taylor, P. W., Jr. and Wurster, D. E.: Dissolution Kinetics of Certain Crystalline Forms of Prednisolone II.

Influence of Low Concentrations of Sodium Lauryl Sulfate, *J. Pharm. Sci. 54*:1654-1658, 1965.

154. Paikoff, M. and Drumm, G.: Method for Evaluating Dissolution Characteristics of Capsules, *J. Pharm. Sci. 54*: 1693-1694, 1965.

155. Levy, G., Leonards, J. R. and Procknall, J. A.: Development of *in Vitro* Dissolution Tests Which Correlate Quantitatively with Dissolution Rate-Limited Drug Absorption in Man, *J. Pharm. Sci. 54*:1719-1722, 1965.

156. Goldberg, A. H., Gibaldi, M., Kanig, J. L. and Schanker, J.: Method for Determining Dissolution Rates of Multiparticulate Systems, *J. Pharm. Sci. 54*:1722-1725, 1965.

157. McClintock, W. J., Swarbrick, J., Christian, J. E. and Banker, G. S.: Nuclear *in Vitro* Method of Continuously Measuring Dissolution Rates, *J. Pharm. Sci. 54*:1782-1786, 1965.

158. Sjogren, J., Solvell, L. and Karlson, I.: Studies on the Absorption Rate of Barbiturates in Man, *Acta Med. Scand. 178*:553-559, 1965.

159. Edmundson, I. C. and Lees, K. A.: A Method for Determining the Solution Rate of Five Particles, *J. Pharm. Pharmacol. 17*:193-201, 1965.

160. Cleave, J. P.: Some Geometrical Considerations Concerning the Design of Tablets, *J. Pharm. Pharmacol. 17*: 698-702, 1965.

161. Randeri, K. J.: Investigation of Certain Tablet Formulation Factors on *in Vitro* Drug Release and *in Vivo* Drug Absorption, *Dissertation Abstr. 25*:7212-7213, 1965.

162. Sekiguchi, K. and Ito, K.: Studies on the Molecular Compounds of Organic Medicinals I. Dissolution Behavior of the Molecular Compound of Sulfanilamide and Sulfathiazole, *Chem. Pharm. Bull. (Tokyo) 13*:405-413, 1965.

163. Doluisio, J. T. and Swintosky, J. V.: Biopharmaceutics, "Remington's Pharmaceutical Sciences," 13th ed., 1965, pp. 380-393.

164. Singh, P., Guillory, J. K., Sokoloski, T. D., Benet, L. Z. and Bhatia, V. H.: Effect of Inert Tablet Ingredients on Drug Absorption I. Effect of Polyethylene Glycol 4000 on the Intestinal Absorption of Four Barbiturates, *J. Pharm. Sci. 55*:63-68, 1966.

165. Bates, T. R., Gibaldi, M. and Kanig, J. L.: Solubilizing Properties of Bile Salt Solutions I. Effect of Temperature and Bile Salt Concentration on Solubilization of Glutethimide, Griseofulvin and Hexestrol, *J. Pharm. Sci. 55*:191-199, 1966.

166. Hamlin, W. E. and Higuchi, W. I.: Dissolution Rate-Solubility Behavior of 3-(1-Methyl-2-pyrrolidinyl)-indole as a Function of Hydrogen Ion Concentration, *J. Pharm. Sci. 55*:205-207, 1966.

167. O'Reilly, R. A., Nelson, E. and Levy, G.: Physiochemical and Physiological Factors Affecting the Absorption of Warfarin in Man, *J. Pharm. Sci. 55*:435-437, 1966.

168. Goldberg, A. H., Gibaldi, M. and Kanig, J. L.: Increasing Dissolution Rates and Gastrointestinal Absorption of Drugs *via* Solid Solutions and Eutectic Mixtures II. Experimental Evaluation of a Eutectic Mixture: Urea-Acetaminophen System, *J. Pharm. Sci. 55*:482-487, 1966.

169. Goldberg, A. H., Gibaldi, M. and Kanig, J. L.: Increasing Dissolution Rates and Gastrointestinal Absorption of Drugs *via* Solid Solutions and Eutectic Mixtures III. Experimental Evaluation of Griseofulvin-Succinic Acid Solid Solution, *J. Pharm. Sci. 55*:487-492, 1966.

170. Ballard, B. E.: Effect of Physical Activity on the Absorption Rate of Procaine Penicillin G Implants, *J. Pharm. Sci. 55*:515-516, 1966.

171. Goldberg, A. H., Gibaldi, M., Kanig, J. L. and Mayersohn, M.: Increasing Dissolution Rates and Gastrointestinal Absorption of Drugs *via* Solid Solutions and Eutectic Mixtures IV. Chloramphenicol-Urea System, *J. Pharm. Sci. 55*:581-583, 1966.

172. Lapidus, H. and Lordi, N. G.: Some Factors Affecting the Release of a Water-Soluble Drug from a Compressed Hydrophilic Matrix, *J. Pharm. Sci. 55*:840-843, 1966.

173. Malone, M., Hochman, H. I. and Nieforth, K. A.: Desoxycholic Acid Enhancement of Orally Administered Reserpine, *J. Pharm. Sci. 55*:972-974, 1966.

174. Desai, S. J., Singh, P., Simonelli, A. P. and Higuchi, W. I.: Investigation of Factors Influencing Release of a Solid Drug Dispersed in Inert Matrices II. Quantitation Procedures, *J. Pharm. Sci. 55*:1224-1229, 1966.

175. Desai, S. J., Singh, P., Simonelli, A. P. and Higuchi, W. I.: Investigation of Factors Influencing Release of Solid Drug Dispersed in Inert Matrices III. Quantitative Studies Involving the Polyethylene Plastic Matrix, *J. Pharm. Sci. 55*:1230-1234, 1966.

176. Desai, S. J., Singh, P., Simonelli, A. P. and Higuchi, W. I.: Investigation of Factors Influencing Release of Solid Drug Dispersed in Inert Matrices IV. Some Studies Involving the Polyvinyl Chloride Matrix, *J. Pharm. Sci. 55*:1235-1239, 1966.

177. Magershohn, M. and Gibaldi, M.: New Method of Solid-State Dispersion for Increasing Dissolution Rates, *J. Pharm. Sci. 55*:1323-1324, 1966.

178. Wagner, J. G.: Design and Data Analysis of Biopharmaceutical Studies in Man, *Can. J. Pharm. Sci. 1*:55-68, 1966.

179. Mitchell, A. G.: Pharmaceutical Factors Affecting Drug Availability, *Australasian J. Pharm. 47*:558-561, 1966.

180. Levy, G.: "Correlation of Gastrointestinal Absorption and *in Vitro* Dissolution Kinetics of Drugs Contained in Oral Dosage Forms," presented at the Eino Nelson Memorial Symposium on Biopharmaceutics, Industrial Pharmacy Section, 113th Annual Meeting of the American Pharmaceutical Association, Dallas, Texas, April 25-29, 1966.

181. Wood, J. H.: "*In Vitro* Evaluation of the Release from Dosage Forms," presented at the Eino Nelson Memorial Symposium on Biopharmaceutics, Industrial Pharmacy Section, 113th Annual Meeting of the American Pharmaceutical Association, Dallas, Texas, April 25-29, 1966.

182. Nogami, H., Nagai, T. and Suzuki, A.: Studies on Powdered Preparations. XVII. Dissolution Rate of Sulfonamides by Rotating Disk Method, *Chem. Pharm. Bull. (Tokyo) 14*:329-338, 1966.

183. Nogami, H., Nagai, T. and Ito, K.: Studies on Powdered Preparations XIX. Dissolution Kinetics of Benzoic Acid Derivatives, *Chem. Pharm. Bull. (Tokyo) 14*:351-357, 1966.

184. Nogami, H., Nagai, T. and Suzuki, A.: Studies on Powdered Preparations XVIII. Dissolution of Sulfadiazine in Various Aqueous Solutions, *Chem. Pharm. Bull. (Tokyo) 14*:339-350, 1966.

185. Wagner, J. G., Gerard, E. S. and Kaiser, D. G.: The Effect of the Dosage Form on Serum Levels of Indoxole, *Clin. Pharmacol. Therap. 7*:610-619, 1966.

186. Yamada, H., Ichihashi, T., Kagisha, F. and Yamamoto, R.: Biopharmaceutical Studies on Factors Affecting Rate of Absorption of Drugs II. Further Investigation of Absorption of Drugs in Micellar Solution, *Chem. Pharm. Bull. (Tokyo) 14*:786-788, 1966.

187. Morrison, B. O.: Tolerance to Oral Hematinic Therapy: Controlled-Release Versus Conventional Ferrous Sulfate, *J. Am. Geriat. Soc. 14*:757-759, 1966.

188. Schwartz, D. E., Vecchio, M., Ronco, A. and Kaiser, K.: Blood Levels After Administration of 7-Chloro-1,3-Dihydro-1-Methyl-5-Phenyl-2H,1,4-Benzodiazepine-2-One (Diazepam) in Various Forms, *Arzneimittel-Forsch. 16*:1109-1110, 1966.

189. Verbist, L. and Dutoit, M.: Ethionamide Blood Levels After Administration of the Drug in Various Pharmaceutical Forms, *Arzneimittel-Forsch. 16*:773-778, 1966.

190. Mellinger, T. J. and Bohorfoush, J. G.: Blood Levels of Dipyridamole (Persantin) in Humans, *Arch. Intern. Pharmacodyn. 163*:471-480, 1966.

191. Varga, F.: Intestinal Absorption of Chloroquine in Rats, *Arch. Intern. Pharmacodyn. 163*:38-46, 1966.

192. Knoechel, E. L., Sperry, C. C. and Lintner, C. J.: Instrumented Rotary Tablet Machines II. Evaluation and Typical Applications in Pharmaceutical Research, Develop-

ment and Production Studies, *J. Pharm. Sci. 56*:116-130, 1967.

193. Higuchi, W. I., Bernardo, P. D. and Mehta, S. C.: Polymorphism and Drug Availability II. Dissolution Rate Behavior of the Polymorphic Forms of Sulfathiazole and Methylprednisolone, *J. Pharm. Sci. 56*:200-207, 1967.

194. Higuchi, W. I.: Diffusional Models Useful in Biopharmaceutics. Drug Release Rate Processes, *J. Pharm. Sci. 56*:315-324, 1967.

195. Marlowe, E. and Shangraw, R. F.: Dissolution of Sodium Salicylate from Tablet Matrices Prepared by Wet Granulation and Direct Compression, *J. Pharm. Sci. 56*:498-504, 1967.

196. Ritschel, W. A. and Orth, H.: Testing of Tablets with Prolonged Action. Enzyme Activity During the Modified Half-Change Method, *J. Pharm. Sci. 56*:773-775, 1967.

197. Niebergall, P. J., Patil, M. Y. and Sugita, E. T.: Simultaneous Determination of Dissolution and Partitioning Rates *in Vitro*, *J. Pharm. Sci. 56*:943-947, 1967.

198. Katchen, B. and Symchowicz, S.: Correlation of Dissolution Rate and Griseofulvin Absorption in Man, *J. Pharm. Sci. 56*:1108-1110, 1967.

199. Levy, G., Leonards, J. R. and Procknall, J. A.: Interpretation of *in Vitro* Dissolution Data Relative to the Gastrointestinal Characteristics of Drugs in Tablets, *J. Pharm. Sci. 56*:1365-1367, 1967.

200. Bates, T. R., Lin, S. L. and Gibaldi, M.: Solubilization and Rate of Dissolution of Drugs in the Presence of Physiologic Concentrations of Lysolecithin, *J. Pharm. Sci. 56*: 1492-1495, 1967.

201. Mitchell, A. G. and Saville, D. J.: The Dissolution of Aspirin and Aspirin Tablets, *J. Pharm. Pharmacol. 19*:729-734, 1967.

202. Levy, G.: "Effect of Dissolution Rate on Absorption, Metabolism and Pharmacologic Activity of Drugs," presented at the 27th International Congress of Pharmaceutical Sciences, Montpellier, France, September 4-9, 1967.

203. Searl, R. O. and Pernarowski, M.: The Biopharmaceutical Properties of Solid Dosage Forms, *Can. Med. Assoc. J. 96*:1513-1520, 1967.

204. Granderton, D. Hadgraft, J. W., Rispin, W. T. and Thompson, A. G.: Break-Up and Dissolution of Phenidione Tablets, *Pharm. Acta Helv. 42*:152-162, 1967.

205. Chapman, R. A.: Biopharmaceutical Properties of Solid Dosage Forms, *Can. Med. Assoc. J. 97*:753-754, 1967.

206. Torrado-Valeiras, J. J.: Sustained Release Theophylline, *Ann. Real Acad. Farm. 33*:581-604, 1967 through *Intern. Pharm. Abstr. 21*:1374C, 1968.

207. Robinson, I. C. and Becker, C. H., Sulfaethylthiadiazole (SETD) Release from Synthetic Wax Prolonged-Release Particles I. Effect of Dispersant Concentration, *J. Pharm. Sci. 57*:49-53, 1968.

208. Singh, P., Desai, S. J., Simonelli, A. P. and Higuchi, W. I.: Role of Wetting on the Rate of Drug Release from Inert Matrices, *J. Pharm. Sci. 57*:213-226, 1968.

209. Schwartz, J. B., Simonelli, A. P. and Higuchi, W. I.: Drug Release from Wet Matrices I. Analysis of Data with First Order Kinetics and with Diffusion-Controlled Model, *J. Pharm. Sci. 57*:274-277, 1968.

210. Schwartz, J. B., Simonelli, A. P. and Higuchi, W. I.: Drug Release from Wax Matrices II. Application of a Mixture Theory to the Sulfonamide-Wax System, *J. Pharm. Sci. 57*:278-282, 1968.

211. Castello, R. A., Jellinek, G., Koniecny, J. M., Kwan, K. C. and Toberman, R. O.: Dissolution Apparatus with Multiple Testing Stations, *J. Pharm. Sci. 57*:485-488, 1968.

212. Gilbaldi, M., Feldman, S. and Bates, T. R.: Correlation of Pharmacologic Activity and Dissolution Rates of Reserpine-Desoxycholic Acid Dispersions, *J. Pharm. Sci. 57*: 708-709, 1968.

213. Gilbaldi, M., Feldman, S., Wynn, R. and Weiner, N. D.: Dissolution Rates in Surfactant Solutions Under Stirred and Static Conditions, *J. Pharm. Sci. 57*:787-791, 1968.

214. Jacob, J. T. and Plein, E. M.: Factors Affecting the Dissolution Rate of Medicaments from Tablets, I. *In Vitro* Dissolution Rate of Commercial Phenobarbital Tablets, *J. Pharm. Sci. 57*:798-801, 1968.

215. Jacob, J. T. and Plein, E. M.: Factors Affecting the Dissolution Rate of Medicaments from Tablets II. Effect of Binder Concentration, Tablet Hardness and Storage Conditions on the Dissolution Rate of Phenobarbital from Tablets, *J. Pharm. Sci. 57*:802-805, 1968.

216. Gibaldi, M. and Weintraub, N.: Dissolution of Salicylic Acid and Polyvinylpyrrolidone from Compressed Mixtures, *J. Pharm. Sci. 57*:832-835, 1968

217. Gibaldi, M., Feldman, S. and Weiner, N. D.: Apparent Non-Steady-State Dissolution Phenomenon in Solutions of Colloidal Solubilizers, *J. Pharm. Sci. 57*:1072-1073, 1968.

218. Lapidus, H. and Lordi, N. G.: Drug Release from Compressed Hydrophilic Matrices, *J. Pharm. Sci. 57*:1292-1301, 1968.

219. Finholt, P. and Solvang, S.: Dissolution Kinetics of Drugs in Human Gastric Juice—The Role of Surface Tension, *J. Pharm. Sci. 57*:1322-1326, 1968.

220. Symchowicz, S. and Katchen, B.: Griseofulvin Absorption in Man After Single and Repeated Treatments and Its Correlation with Dissolution Rates, *J. Pharm. Sci. 57*:1383-1386, 1968.

221. Pernarowski, M., Woo, W. and Searl, R. O.: Continuous Flow Apparatus for the Determination of the Dissolution Characteristics of Tablets and Capsules, *J. Pharm. Sci. 57*:1419-1421, 1968.

222. Wiseman, E. H. and Federici, N. J.: Development of a Sustained-Release Aspirin Tablet, *J. Pharm. Sci. 57*:1535-1539, 1968.

223. Simonelli, A. P., Flanagan, D. R. and Higuchi, W. I.: Apparent Discrepancy Between Theory and Experimental Data for Dissolution from the Rotating Disk Under Stirred and Unstirred Condition, *J. Pharm. Sci. 57*:1629-1631, 1968.

224. McClintock, W. J., Kildsig, D. O., Kessler, W. V. and Banker, G. S.: Nuclear *in Vitro* Method of Continuously Evaluating Release Rates of Solid Dosage Forms, *J. Pharm. Sci. 57*:1649-1652, 1968.

225. Raghunathan, Y. and Becker, C. H.: Spray-Congealed Formulations of Sulfaethidole (SETD) and Waxes for Prolonged-Release Medication. Effect of Modifiers, *J. Pharm. Sci. 57*:1748-1755, 1968.

226. Aguiar, A. J., Wheeler, R. M., Fusari, S. and Zelmer, J. E.: Evaluation of Physical and Pharmaceutical Factors Involved in Drug Release and Availability from Chloramphenicol Capsules, *J. Pharm. Sci. 57*:1844-1850, 1968.

227. Lin, S. G., Menig, J. and Lachman, L.: Interdependence of Physiologic Surfactant and Drug Particle Size on the Dissolution Behavior of Water-Soluble Drugs, *J. Pharm. Sci. 57*:2143-2148, 1968.

228. Simonelli, A. P., Mehta, S. C. and Higuchi, W. I.: "Dissolution Rates of High Energy Polyvinylpyrrolidone (PVP)-Sulfathiazole Coprecipitates," presented at Meeting of the APhA Academy of Pharmaceutical Sciences, Miami Beach, Florida, May 5-10, 1968.

229. Levy, G.: "Kinetics and Implications of Dissolution Rate-Limited Gastrointestinal Absorption of Drugs, Physico-Chemical Aspects of Drug Actions," Vol. 7, Pergamon Press, New York, 1968, pp. 33-62.

230. Polderman, J. and Braakman, D. R.: The Relation Between Compression Force and Dissolution Time of Tablets, *J. Pharm. Pharmacol. 20*:323-324, 1968.

231. Nixon, J. J., Khalig, S. A. H. and Carless, J. E.: Gelatin Coacervate Micro Capsules Containing Sulphamerazine: Their Preparation and the *in Vitro* Release of the Drug, *J. Pharm. Pharmacol. 20*:528-538, 1968.

232. Carless, J. E., Moustafia, M. A. and Rapson, H. D. C.: Effect of Crystal Form, Cortisone Alcohol and Agitation on Crystal Growth of Cortisone Acetate in Aqueous Suspensions, *J. Pharm. Pharmacol. 20*:639-645, 1968.

233. Carless, J. E., Moustafia, M. A. and Rapson, H. D.: Dissolution and Crystal Growth in Aqueous Suspensions of

Cortisone Acetate, *J. Pharm. Pharmacol. 20*:630-638, 1968.

234. Elworthy, P. H. and Lipscomb, F. J.: The Effect of Some Non-Ionic Surfactants and a Polyoxyethylene Glycol on the Dissolution Rate of Griseofulvin, *J. Pharm. Pharmacol. 20*:923-933, 1968.

235. Walters, V.: The Dissolution of Paracetamol Tablets and the *in Vitro* Transfer of Paracetamol with and without Sorbitol, *J. Pharm. Pharmacol. 20*:228S-231S, 1968, No. 12 (Suppl.).

236. Barzilay, R. R. and Hersey, J. A.: Dissolution Rate Measurements by Automated Dialysis Method, *J. Pharm. Pharmacol. 20*:2325-2385, 1968, No. 12 (Suppl.).

237. Poole, J. W., Owen, G., Silverio, J., Freyhof, J. H. and Roseman, S. B.: Physiochemical Factors Influencing the Absorption of the Anhydrous and Trihydrate Forms of Ampicillin, *Current Therap. Res. 10*:292-303, 1968.

238. Thomas, D. G. and Armstead, R. A.: Concentration-Gradient-Driven Convection: Experiments, *Science 160*:995-996, 1968.

239. Tannenbaum, P. J., Rosen, E., Flanagan, T. and Crosley, A. P.: The Influence of Dosage Form on the Activity of a Diuretic Agent, *Clin. Pharmacol. Therap. 9*: 598-604, 1968.

240. Epstein, L. C. and Lasagna, L.: A Comparison of the Effects of Orally Administered Barbiturate Salts and Barbituric Acids on Human Psychomotor Performance, *J. Pharmacol. Exptl. Therap. 164*:433-441, 1968.

241. Glazko, A. J., Kinkel, A. W., Aleghani, W. C. and Holmes, E. L.: An Evaluation of the Absorption Characteristics of Different Chloramphenicol Preparations in Normal Human Subjects, *Clin. Pharmacol. Therap. 9*:472-483, 1968.

242. Wagner, J. G., Novak, E., Patel, N. C., Chidester, C. G. and Lummis, W. L.: Absorption, Excretion and Half-Life of Clinimycin in Normal Adult Males, *Am. J. Med. Sci. 256*:25-37, 1968.

243. Tawaski, L.: Aspirin: Dissolution Rates of Two Polymorphic Forms, *Science 160*:76, 1968.

244. Torrado-Valeiras, J. J.: Sustained Release Theophylline, *Ann. Real Acad. Farm. 33*:581-604, 1967; through *Intern. Pharm. Abstr. 21*:1374c, 1968.

245. Laine, V., Strandman, D. and Tikkanen, R.: Enteric Coated Tablets and the Salicylate Concentrations in the Plasma in the Morning, *Svenska Läkartidr. 65*:3832-3837, through *Intern. Pharm Abstr. 5*:1519, 1968.

246. Tannenbaum, P. J., Rosen, E., Flanagan, T. and Crosley, A. P., Jr.: The Influence of Dosage Form on the Activity of a Diuretic Agent, *Clin. Pharmacol. Therap. 9*: 598-604, 1968.

247. Elworthy, P. H. and Lipscomb, F. J.: The Effect of Some Non-Ionic Surfactants and a Polyoxyethylene Glycol on the Dissolution Rate of Griseofulvin, *J. Pharm. Pharmacol. 20*:923-933, 1968.

248. Ferrari, A. and Khoury, A. J.: A New Concept for Automated Drug-Dissolution Study, *Ann. N.Y. Acad. Sci. 153*:660, 1968, Art. 2.

249. Hersey, J. A. and Barzilay, R. B.: Dissolution Rates of Sparingly Soluble Tablets, *J. Pharm. Pharmacol. 21*:65-71, 1969.

250. Nogami, H., Hagai, T., Fukuoka, E. and Yotsuyamagi, T.: Dissolution Kinetics of Barbital Polymorphs, *Chem. Pharm. Bull. (Tokyo) 17*:23-31, 1969.

251. Fosdick, W. M. and Shephard, W. L.: Enteric Coated Microspherules, A Clinical Appraisal of Two Forms of Aspirin, *J. Clin. Pharmacol. J. New Drugs 9*:126-129, 1969.

252. Nogami, H., Nagai, T. and Yotsuyamagi, T.: Dissolution Phenomena of Organic Medicinals Involving Simultaneous Phase Changes, *Chem. Pharm. Bull. (Tokyo) 17*: 499-509, 1969.

253. Brice, G. W. and Hammer, H. F.: Therapeutic Nonequivalence of Oxytetracycline Capsules, *J. Am. Med. Assoc. 208*:1189-1190, 1969.

254. Castle, W. B., Astwood, E. R., Finland, M. and Keefer, C. S.: White Paper on the Therapeutic Equivalence of Chemically Equivalent Drugs, *J. Am. Med. Assoc. 208*: 1171-1172, 1969.

255. Thakker, A. L. and Hall, N. A.: Micellar Solubilization of Testosterone III. Dissolution Behavior of Testosterone in Aqueous Solutions of Selected Surfactants, *J. Pharm. Sci. 58*:68-71, 1969.

256. Kornblum, S. S.: Sustained-Action Tablets Prepared by Employing a Spray-Drying Technique for Granulation, *J. Pharm. Sci. 58*:125-127, 1969.

257. Gibaldi, M., Feldman, S. and Weiner, N. D.: Dissolution Kinetics in Micellar Solutions Under Nonsink Conditions, *J. Pharm. Sci. 58*:132-133, 1969.

258. Garrett, E. R.: Physico-Chemical Factors—Drug Systems Affecting Availability and Reliability of Response, *J. Am. Pharm. Assoc. NS9*:110-112,134, 1969.

259. Taraszka, M. J. and Delor, R. A.: Effect of Dissolution Rate of Sulfamethazine from Tablets on Absorption and Excretion of Sulfamethazine, *J. Pharm. Sci. 58*:207-210, 1969.

260. Sjuib, F., Simonelli, A. P. and Higuchi, W. I.: Release of Mixtures of Two Amphoteric Drugs, Sulfadiazine and Sulfapyridine, from Inert Matrices into Reacting Media, Abstract No. 48*.

261. Sjuib, F., Simonelli, A. P. and Higuchi, W. I.: Release of Drug From Reactive Mixtures in Inert Matrices, Abstract No. 49*.

262. Tingstad, J. E. and Riegelman, S.: Dissolution Rate Studies I. Design of Continuous Flow Apparatus, Abstract No. 50*.

263. Wagner, J. G.: Interpretation of Percent Dissolved-Time Plots Derived from *in Vitro* Testing of Conventional Tablets and Capsules, Abstract No. 51*.

264. Samyn, J. C. and Jung, W. Y.: *In Vitro* Dissolution from Several Experimental Capsule Formulations, Abstract No. 52*.

265. Poole, J. W. and Bahal, C. K.: Dissolution Behavior and Solubility of the Anhydrous and Dihydrate Forms of WY-4508, an Aminosalicylic Penicillin, Abstract No. 53*.

266. Piccolo, J. and Tawashi, R.: Inhibited Dissolution of Drug Crystals by a Certified Water-Soluble Dye, Abstract No. 54*.

267. Bates, T. R., Lambert, D. A. and Johns, W. H.: Correlation Between the Rate of Dissolution and Absorption of Salicylamide from Tablet and Suspension Dosage Forms, Abstract No. 110*.

268. Rosen, E.: Principles of Formulation *in Vitro, Australasian J. Pharm. 74*:525-531, 1969 (Sci. Suppl.).

269. Blythe, R. H.: "A Systematic Approach to Bioavailability Testing," presented at the Meeting of the National Association of Pharmaceutical Manufacturing, Miami, Florida, on May 30, 1969.

270. Rippie, E. G. and Johnson, J. R.: Regulation of Dissolution Rate by Pellet Geometry, *J. Pharm. Sci. 58*:428-431, 1969.

*Abstracts, Symposia and Contributed Papers Presented to the APhA Academy of Pharmaceutical Sciences at the 116th Annual Meeting of the American Pharmaceutical Association, Montreal, Canada, May 17-23, 1969.

CHAPTER 21

Quantitative Correlations of in Vivo Data with in Vitro Rate of Dissolution Data

In the previous Chapter 20, several examples of rank order correlations of *in vivo* with *in vitro* data were presented. In this chapter several examples of quantitative correlations of *in vivo* with *in vitro* data will be presented. As formerly stated, a quantitative correlation is one in which the *in vivo* variable may be related to the *in vitro* variable by means of an equation. Frequently the equation is not given *per se* but is implicit in a graph. For example, if the variables are plotted and a straight line is drawn through the points then the variables are related by the equation of a straight line, namely $Y = aX$ or $Y = aX + b$. Here Y is the variable plotted on the ordinate, X is the variable plotted on the abscissa, "a" is the slope of the line and "b" is the intercept of the line on the ordinate axis.

Penicillin V

Figure 21.1 shows the correlation of blood level results in fasting human subjects administered the potassium salt, the calcium salt and the free acid form of penicillin V orally in powdered form with *in vitro* rates of dissolution. Here Y *versus* X is a plot of average plasma concentration at 0.5 hour post administration against the concentration of penicillin V in solution after 10 minutes *in vitro* at *p*H 2.0 on a logarithmic scale. Y′ *versus* X is a plot of average area under the plasma level curves of the 10 subjects against the concentration of penicillin V in solution after 10 minutes *in vitro* at *p*H 2.0 on a logarithmic scale. Y′ *versus* X′ is a plot of average area under the plasma level curves of the 10 subjects against the concentration of penicillin V in solution after 10 minutes *in vitro* at *p*H 8.0 on a logarithmic scale. In each case the points from left to right refer to penicillin V acid, calcium penicillin V and potassium penicillin V. These plots were prepared by the author from the original data of Juncher and Raaschou (1957).

Amphetamine

Figure 21.2 shows a correlation of percent amphetamine released *in vitro* in one hour with *in vivo* availability in man for seven different brands of so-called sustained release capsules containing coated pellets of amphetamine. Of eight products tested F and H exhibited essentially constant urinary excretion rates for 20 to 24 hours, respectively, and were fully available. The other six products showed little or no prolonged or sustained action and/or were not fully available. The figure was reproduced from the paper of Shenoy *et al.* (1959). It is the author's opinion that the *in vivo* variable in such plots should be plotted on the ordinate and the *in vitro* variable on the abscissa. To conform to this the variable, *in vivo* availability, should have been plotted on the ordinate in Figure 21.2 and the variable, percent released *in vitro* in one hour, should have been plotted on the abscissa. This is in keeping with the concept that the dependent variable should be plotted on the ordinate and the independent variable should be plotted on the abscissa.

Prediction of Average Plasma Concentrations of HT 1479

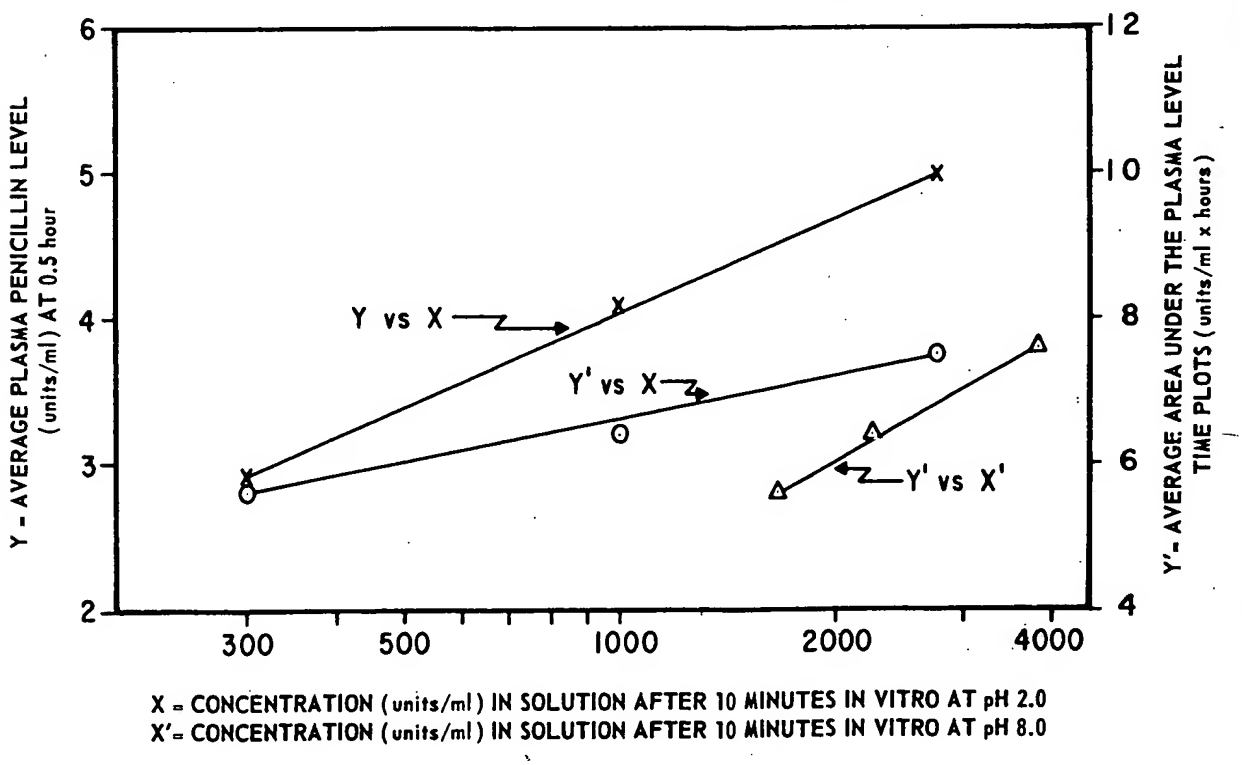
The solid circles in Figure 21.3 are average plasma concentrations of the free base of HT 1479 [1-(o-methoxyphenyl)-4-(γ-methoxypropyl) - piperazine phosphate] in six dogs following oral administration of 39.5 mg of the salt per Kg of body weight, equivalent to 28.8 mg of the free base per Kg of body weight, in aqueous solution. The line through these points in the figure is based on the equation:

$$C' = \frac{a_o\, k_a}{V_d\,(k_d - k_a)}\,[e^{-k_a t} - e^{-k_d t}] \qquad \text{Eq. 21.1}$$

Equation 21.1 corresponds to the model:

Solution of drug at absorption sites $\xrightarrow{k_a}$ Blood and other fluids of distribution $\xrightarrow{k_d}$ Drug in urine + metabolic products

Figure 21.1. Correlation of blood level results in fasting human subjects administered the potassium salt, the calcium salt and the free acid form of penicillin V orally in powdered form with *in vitro* rates of dissolution. See text for explanation. Original data were taken from Juncher and Raaschou (1957)



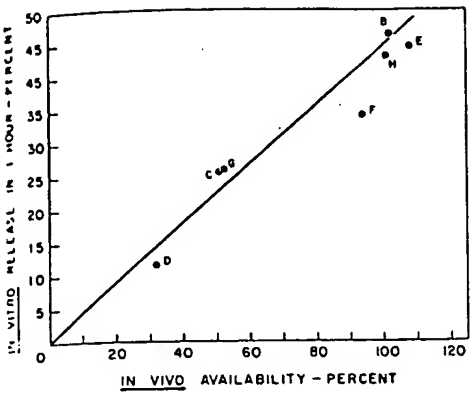


Figure 21.2. Correlation of percent amphetamine released *in vitro* in one hour with *in vivo* availability for seven different brands of so-called sustained-release capsules containing coated pellets of amphetamine. From Shenoy *et al.* (1959), reproduced with permission of the copyright owner

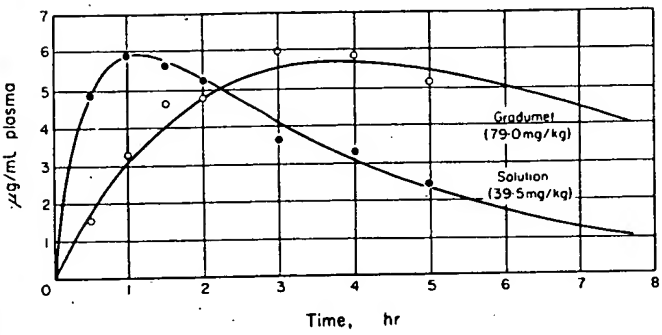
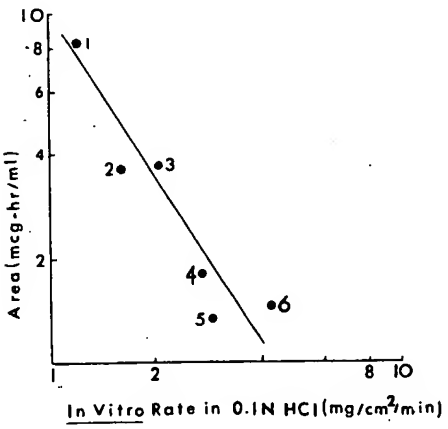


Figure 21.3. Prediction of average plasma levels of HT 1479 in six dogs following oral administration of the drug as a sustained-release tablet (Gradumet). See text for explanation. Reprinted with permission of Wiegand and Taylor (1960) and Pergamon Publishing Company

Figure 21.4. Showing the relationship between the area under the erythromycin blood level curve and the rate of dissolution of erythromycin and several of its esters in 0.1 N hydrochloric acid. See text for explanation. The figure was re-drawn from Fig. 2 of Nelson (1962) and is reproduced with permission of the editor of *Chem. Pharm. Bull. (Tokyo)*



Sustained-release (Gradumet) tablets, containing the same drug, were tested *in vitro* and the data were found to conform to Equation 21.2.

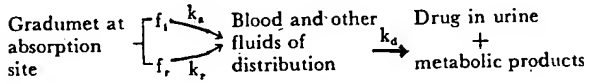
$$a_r = a_o f_i + a_o f_r (1-e^{-k_r t}) \qquad \text{Eq. 21.2}$$

Here, a_r is the fraction of drug released at time t, $a_o = 1$, f_i is the fraction of drug apparently released instantaneously, f_r is the fraction of drug released exponentially and k_r is the first order rate constant for the release process.

Based on the *in vivo* solution data and the *in vitro* release rate data the average plasma level, C, expected following administration of the sustained-release tablet to the same six dogs, is given by Equation 21.3.

$$C = \frac{a_o f_r k_a k_r}{V_d (k_a - k_r)(k_d - k_r)} [e^{-k_r t} - e^{-k_d t}] + \frac{a_o f_i k_a - \frac{a_o f_r k_a k_r}{(k_a - k_r)}}{V_d (k_d - k_a)} [e^{-k_a t} - e^{-k_d t}] \qquad \text{Eq. 21.3}$$

Equation 21.3 is based on the model:



The open circles in Figure 21.3 are average plasma concentrations of HT 1479 free base observed in the six dogs following oral administration of 79.0 mg salt per Kg body weight, equivalent to 57.6 mg free base per Kg of body weight. The line drawn through the points was derived using Equation 21.3 and the following values of the constants derived from the solution dose and the *in vitro* testing:

$k_a = 2.0\ hr^{-1}$, $k_d = 0.28\ hr^{-1}$, $V_d = 3.52$ L/Kg, $a_o = 57.6$ mg/Kg, $k_r = 0.25\ hr^{-1}$, $f_i = 0.12$ and $f_r = 0.88$.

It should be noted that the values of f_i, f_r and k_r used in fitting the average plasma concentrations following the sustained-release tablet with Equation 21.3 were derived from the *in vitro* release rate test; this strongly suggests that the release characteristics of the sustained-release tablet *in vivo* were essentially the same as *in vitro*. This interesting correlation was reported by Weigand and Taylor (1960).

Erythromycin

Figure 21.4 shows the relationship between the area under erythromycin blood level curves and the rate

of dissolution of erythromycin and several of its esters in 0.1 N hydrochloric acid. The numbers on the points refer to the compounds as follows: 1-erythromycin propionate; 2-erythromycin acetate; 3-erythromycin acrylate; 4-erythromycin isobutyrate; 5-erythromycin butyrate; 6-erythromycin. The dissolution rates were obtained by compressing disks of the compound at high pressure and rotating the disks, with only one face exposed, in a brass holder at the end of a stirring shaft, rotating at 500 r.p.m., in the dissolution medium.

Figure 21.5 shows the relationship between the area under erythromycin blood level curves and the rate of dissolution of several erythromycin esters in 0.1 M borate buffer, *p*H 7.4. The numbers refer to the same compounds as indicated above in the text pertaining to Figure 21.4. The dissolution rates in borate buffer were also determined by the rotating disk method as described above.

Figures 21.4 and 21.5 were re-drawn from the originals reported by Nelson (1962). In acid solution the area is inversely related to rate of dissolution; since the area under the blood concentration curve is indicative of amount absorbed (if it is assumed the plasma clearance is constant), then the more slowly dissolving the erythromycin ester in acid the greater the amount of drug eventually absorbed. This is due to the fact that erythomycin is degraded to inactive products by acid. For some of the esters, but not for erythromycin or its acetate, the area under the blood level curve was directly proportional to the rate of dissolution in *p*H 7.4 borate buffer. In this series of compounds erythromycin propionate gave the greatest area under the blood level curve; this apparently is caused by its very slow dissolution in acid in the stomach, thus conserving the dose, and its high rate of dissolution in less acidic or alkaline fluids once the compound reaches the small intestine.

Acetylsalicylic Acid

Figure 21.6 shows the relationship between the mean amount of apparent salicylate excreted in the urine in one hour after administration of two 5 grain tablets and the amount of aspirin dissolved in ten minutes from one tablet in an *in vitro* test. Two essentially parallel lines were obtained for group A and B. The line for group B (10 subjects) was displaced higher than the line for group A (14 subjects). The protocols were the same except that group A ingested the tablets followed by 100 ml of water while group B ingested the tablets followed by 200 ml of water. Each set of three points represent three different commercial brands of aspirin tablets. The figure is reproduced from the work of Levy (1961).

Figure 21.7 shows the relationship between serum salicylate concentrations in man and percentage of drug dissolved *in vitro* in a given time. Each serum salicylate point is the average of between 20 and 40 people who took two 5 grain aspirin tablets. The *in vitro* stirring rate was 440 r.p.m.

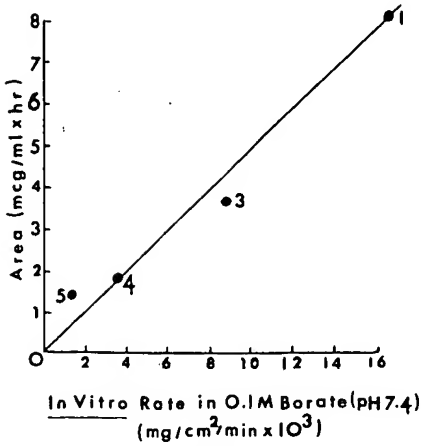


Figure 21.5. Showing the relationship between the area under the erythomycin blood level curve and the rate of dissolution of several erythromycin esters in 0.1 N borate buffer, *p*H 7.4. See text for explanation. The figure was re-drawn from Fig. 3 of Nelson (1962) and is reproduced with permission of the editor of *Chem. Pharm. Bull. (Tokyo)*

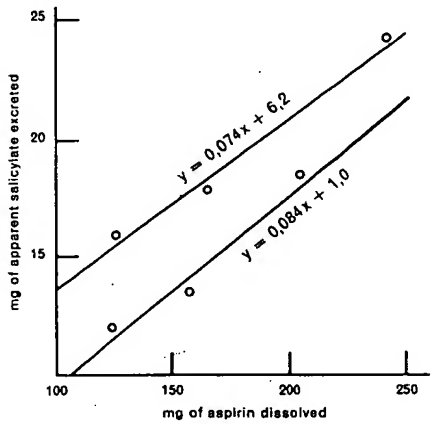
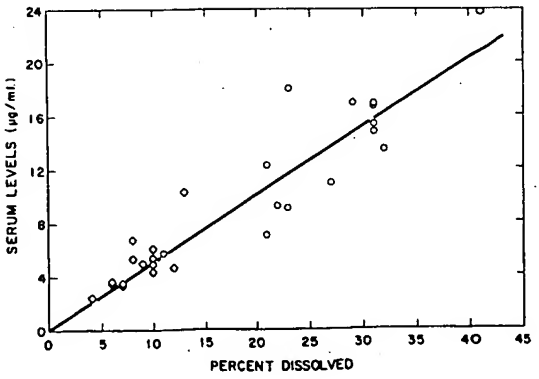


Figure 21.6. Relationship between the mean amount of apparent salicylate excreted in one hour after administration of two 5 grain aspirin tablets and the amount of aspirin dissolved in ten minutes from one tablet in an *in vitro* test. See text for explanation. From Levy (1961) reproduced with permission of the copyright owner

Figure 21.7. Relationship between serum salicylate concentrations in man and percentage of drug dissolved *in vitro*. Key: ◊ 10 min. serum concentration and percentage dissolved in 0.3 min.; ○ 20 min. serum concentration and percentage dissolved in 1.0 min. From J. H. Wood, *Pharm. Acta Helv.* 42:129-151, 1967, with permission of the editor



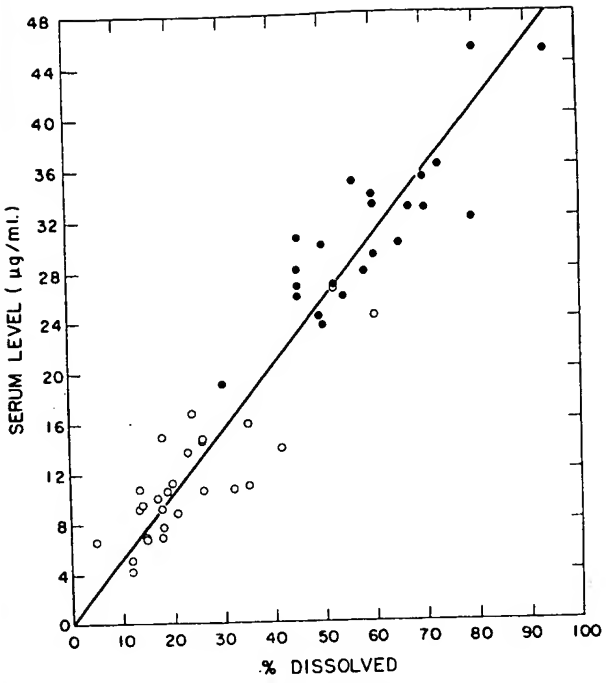


Figure 21.8. Relationship between serum salicylate concentrations in man and percentage of drug dissolved *in vitro*. Key: ○ 10 min. serum concentration and percentage dissolved in 1.2 min.; ● 20 min. serum concentration and percentage dissolved in 4.2 min. From J. H. Wood *Pharm. Acta Helv.* 42:129-151, 1967, with permission of the editor

Figure 21.9. Correlation of percent aspirin absorbed at time T (estimated by method of Wagner and Nelson, 1963) with percent aspirin dissolved *in vitro* at time (T-log time)/I for absorption from solution, plain tablets and microencapsulated particles. See text for explanation. From Levy *et al.* (1965), reproduced with permission of the copyright owner

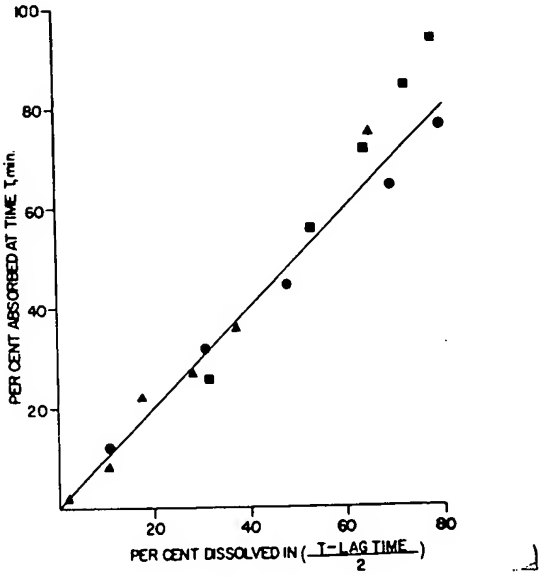


Figure 21.8 shows the relationship between serum salicylate concentrations in man and percentage of drug dissolved *in vitro* in a given time. Each serum salicylate point is the average of between 20 and 40 people who took two tablets containing 5 grains of aspirin and an antacid mixture of magnesium carbonate and dihydroxy aluminum glycinate (Bufferin tablets). The *in vitro* stirring rate was 440 r.p.m. Figures 21.7 and 21.8 were taken from the excellent review of Wood (1967).

Levy and Hollister (1964) introduced a new method of correlating *in vivo* and *in vitro* data and the method was further elaborated by Levy, Leonards and Procknall (1965) and Levy (1968). To apply this method Levy *et al.* first estimate the percent of drug absorbed in a given time by applying the method of Wagner and Nelson (1963). The logarithm of the percent not absorbed is then plotted *versus* time. If a straight line is obtained on this plot the line is extrapolated back to the time when the ordinate is the logarithm of 100 and this time is taken as the lag time. The slope of this straight line gives the *in vivo* "absorption rate constant." The intensity factor, I, is given by Equation 21.4 if kinetics of absorption are apparent first order or by Equation 21.5 if the kinetics of absorption and/or dissolution *in vitro* are not apparent first order.

$$I = \frac{\text{Apparent first order rate constant for dissolution in vitro}}{\text{Apparent first order rate constant for absorption in vivo}} \qquad \text{Eq. 21.4}$$

$$I = \frac{\text{Time required for 50\% absorption in vivo}}{\text{Time required for 50\% absorption in vitro}} \qquad \text{Eq. 21.5}$$

To correlate the *in vivo* with *in vitro* data the percent of the dose absorbed to each time, T, is plotted against the percent dissolved *in vitro* at time (T-lag time)/I. This type of plot yields a regression line with slope equal to unity and passing through the origin. Figure 21.9 shows an example of such plot, taken from Levy *et al.* (1965), and refers to absorption of aspirin from solution, plain tablets and microencapsulated particles. In this case the intensity factor is 2 (*i.e.*, I=2). The *in vitro* dissolution conditions were those of Levy and Hayes (1960) employing 0.1 N hydrochloric acid at 37°C and a 50 r.p.m. stirring rate. Figure 21.10 is another example of such a plot where the lag time was not subtracted causing an intercept. The ordinate values in Figure 21.10 were based on an average of 30 determinations of plasma salicylate concentrations in 15 subjects following oral ingestion of 975 mg of aspirin as three tablets. In this case the intensity factor was 8.5 reflecting a more intensive agitation of the dissolution medium.

The method of Wagner and Nelson (1963) to estimate percent of drug absorbed is based on the one compartment open model and may give biased estimates. One could also fit plasma concentration data to the two compartment open model with first order absorption and use the estimated first order rate constant for absorption or the corresponding time for 50

percent absorption to calculate the intensity factor by means of Equations 21.4 and 21.5.

Benzphetamine and Etryptamine Salts

Salt formation as a potential means of obtaining sustained release or prolonged action was studied and an interesting correlation resulted from the work of Morozowich *et al.* (1962). As an *in vivo* parameter the LT_{50} (lethal time for 50 percent of the animals) in mice was estimated when a dose equivalent to 400 mg/Kg of benzphetamine hydrochloride or 125 mg/Kg of etryptamine acetate (the doses which just produced 100 percent deaths) was administered as the free base or salt to each of ten mice. *In vitro* rates of dissolution of the compounds were determined by the hanging pellet method of Nelson (1958b). The hydrochloride, diliturate, polygalacturonate, 8-nitrotheophyllinate, barbiturate, methylene-bis-salicylate, 2,4-dihydrobenzoate and pamoate salts of benzphetamine were studied. The free base and the acetate, 8-chlortheophyllinate, barbiturate, pamoate and 8-nitrotheophyllinate salts of etryptamine were studied.

Figure 21.11 is a log-log plot of the LT_{50} in mice against the equivalent dissolution rate at *p*H 7.2 (mg free base/cm²/hr) at 37° for all the compounds tested. The line drawn through the points has a slope of −0.5 suggesting that the LT_{50} is inversely related to the square root of the equivalent rate of dissolution measured *in vitro*. This figure is taken from the paper of Morozowich *et al.* (1962).

Figure 21.12 is a plot of the logarithm of the LT_{50} in mice against the logarithm of the equivalent rate of dissolution at *p*H 7.2 (mg free base/cm²/hr) at 37° and is based on the same data as shown in Figure 21.11. In this case the points for benzphetamine hydrochloride and etryptamine acetate were omitted in estimating the regression line with Equation 21.6

$$\log LT_{50} = 1.6755 - 0.6276 \log R \qquad \text{Eq. 21.6}$$

where R is the *in vitro* rate of dissolution. Hence in this case the slope of the line is −0.6276 compared with −0.5 in Figure 21.11. The reason for excluding the points corresponding to benzphetamine hydrochloride and etryptamine acetate is based on theory developed by Di Santo and Wagner (1969) and the fact that these two salts had the highest rates of dissolution hence the availability of the active bases to the receptors in the mice from these two salts may not have been rate-limited by dissolution. Figure 21.12 is taken from Di Santo and Wagner, (1969).

Tolbutamide

The blood sugar response to tolbutamide is markedly influenced by the composition and method of manufacture of compressed tablets of the drug. This is illustrated by Figure 21.12, reproduced from Wagner (1966). In this figure the ordinate (Y value) is the adjusted average blood sugar as a percent of the placebo group average at one hour post administration; on the abscissa is plotted the time for 20 percent of the

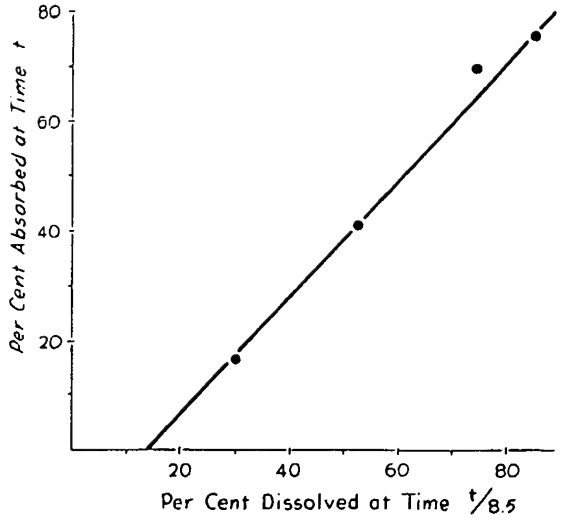
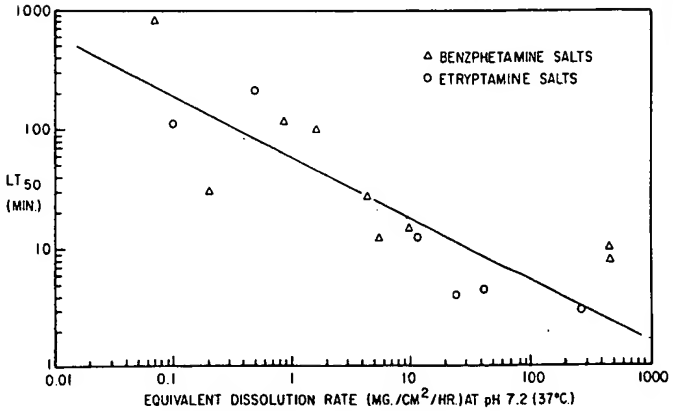


Figure 21.10. Correlation of percent aspirin absorbed at time T (estimated by method of Wagner and Nelson, 1963) with percent aspirin dissolved *in vitro* at time T/8.5. See text for explanation. Reprinted with permission of Levy (1966) and Pergamon Publishing Company

Figure 21.11. Log-log plot of LT_{50} in mice against equivalent dissolution rate of pH 7.2 for etryptamine and benzphetamine salts. Key: △ -benzphetamine salts; ○ etryptamine and its salts. See text for explanation. From Morozowich *et al.* (1962), reproduced with permission of the copyright owner



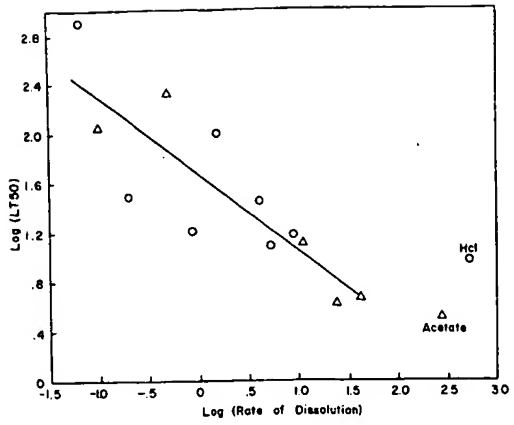
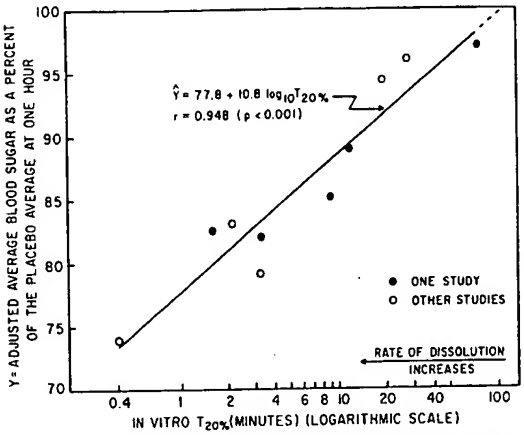


Figure 21.12. Log-log plot of LT_{50} in mice against equivalent dissolution rate at pH 7.2 for etryptamine and benzphetamine salts. Key: ○ -benzphetamine salts; △ -etryptamine free base and four of its salts. See text for explanation. Original data of Morozowich *et al.* (1962) as re-evaluated by DI Santo and Wagner, *J Pharm. Sci.* 58:1077-1085, 1969. Reproduced with permission of the copyright owner

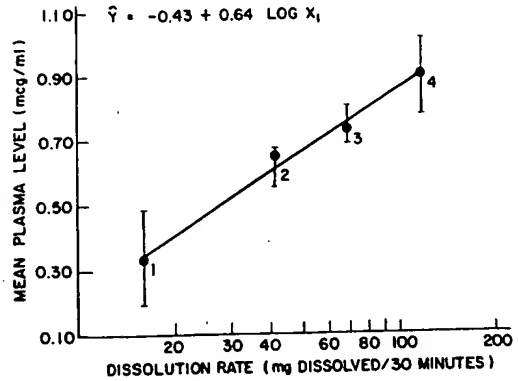


RELATIONSHIP BETWEEN BLOOD SUGAR LEVEL AT ONE HOUR AND TIME FOR 20% OF THE TOLBUTAMIDE TO DISSOLVE FROM THE DOSAGE FORM IN VITRO

Figure 21.13. Correlation between the adjusted average blood sugar level in normals at one hour post administration (expressed as a percent of the placebo group average) with time for 20 percent of the drug to dissolve in an *in vitro* test (on a logarithmic scale) for ten different types of tolbutamide tablets. From Wagner (1966) with permission of the *Canadian Journal of Pharmaceutical Sciences*

Figure 21.14. Correlation of average plasma concentrations of griseofulvin after a single oral dose of 500 mg in 10 healthy subjects with the amount of griseofulvin dissolved in 30 minutes in simulated intestinal fluid for four different griseofulvin preparations. From Katchen and Symchowicz (1967), reproduced with permission of the copyright owner

CORRELATION OF DISSOLUTION RATE AND MEAN GRISEOFULVIN PLASMA LEVEL



tolbutamide to dissolve in an *in vitro* test on a logarithmic scale. The points represent ten different types of tolbutamide tablets. The solid point to the top right of the figure represents a compressed disk of tolbutamide without additives and this "tablet" essentially had no blood sugar lowering properties at all in man despite the fact that 1.0 gram of pure tolbutamide was administered in this form to the human subjects in the *in vivo* studies.

Griseofulvin

Figure 21.14 is a plot of mean plasma concentration of griseofulvin after a single 500 mg dose of griseofulvin was administered to each of 10 human subjects against the amount of griseofulvin dissolved in 30 minutes in simulated intestinal fluid *in vitro*. The four points represent four different griseofulvin preparations. The figure is reproduced from the report of Katchen and Symchowicz, (1967).

Aminorex-C^{14}

Figure 21.15 is a correlation of times required for 25 percent and 50 percent absorption in man with times for 25 percent and 50 percent dissolution *in vitro* for six different dosage forms containing aminorex-C^{14}, the labeled compound corresponding to 2-amino-5-phenyl-2-oxozoline (Apiquel-McNeil Laboratories). The times required for 25 percent and 50 percent absorption were estimated by the method of Wagner and Nelson (1963) which may not be strictly valid since total radioactivity was measured in plasma and urine and at least one or more metabolites were known to exist. The figure is taken from the report of Cressman *et al.* (1969)

Salicylamide

Figure 21.16 shows a correlation between the mean cumulative percent of the dose of salicylamide excreted in the urine of four human volunteers in one hour and the percent salicylamide in solution after 15 minutes and after 20 minutes *in vitro*. Three different dosage forms of salicylamide—an experimental tablet, a commercial tablet and a commercial suspension—are represented by the points. The figure is reproduced from the report of Bates *et al.* (1969)

References

1. Juncher, H. and Raaschou, F.: The Solubility of Oral Preparations of Penicillin V, *Antibiotic Med. Clin. Therapy* 4:497-507, 1957.

2. Shenoy, K. G., Chapman, D. G. and Campbell, J. A.: Sustained Release in Pelleted Preparations as Judged by Urinary Excretion and *in Vitro* Methods, *Drug. Std.* 27:77-84, 1959.

3. Wiegand, R. G. and Taylor, J. D.: Kinetics of Plasma

Drug Levels After Sustained Release Dosage, *Biochem. Pharmacol.* *3*:256-263, 1960.

4. Nelson, E.: Physiochemical Factors Influencing the Absorption of Erythromycin and Its Esters, *Chem. Pharm. Bull. (Tokyo)* *10*:1099-1101, 1962.

5. Levy, G.: Comparison of Dissolution and Absorption Rates of Different Commercial Aspirin Tablets, *J. Pharm. Sci.* *50*:388-392, 1961.

6. Wood, J. H.: *In Vitro* Evaluation of Physiological Availability of Compressed Tablets, *Pharm. Acta Helv.* *42*: 129-151, 1967.

7. Levy, G. and Hollister, L. E.: Inter- and Intrasubject Variation in Drug Absorption Kinetics, *J. Pharm. Sci.* *53*: 1446-1453, 1964.

8. Levy, G., Leonards, J. R. and Procknall, J. A.: Development of *in Vitro* Dissolution Tests Which Correlate Quantitatively with Dissolution Rate-Limited Drug Absorption in Man, *J. Pharm. Sci.* *54*:1719-1722, 1965.

9. Levy, G.: Kinetics and Implications of Dissolution Rate Limited Gastrointestinal Absorption of Drugs, Proceedings of the 3rd International Pharmacological Meeting, July 24-30, 1966, Volume 7, Physico-Chemical Aspects of Drug Actions, Pergamon Press, New York, 1968, p. 33-62.

10. Wagner, J. G. and Nelson, E.: Percent Absorbed Time Plots Derived from Blood Level and/or Urinary Excretion Data, *J. Pharm. Sci.* *52*:610-611, 1963.

11. Levy, G. and Hayes, B. A.: Physiochemical Basis of the Buffered Acetylsalicylic Acid Controversy, *New Engl. J. Med.* *262*:1053-1058, 1960.

12. Morozowich, W., Chulski, T., Hamlin, W. E., Jones, P. M., Northam, J. I., Purmalis, A. and Wagner, J. G.: Relationship Between *in Vitro* Dissolution Rates, Solubilities and LT_{50}'s in Mice of Some Salts of Benzphetamine and Etryptamine, *J. Pharm. Sci.* *51*:993-996, 1962.

13. Nelson, E.: Dissolution Rate of Mixtures of Weak Acids and Tribasic Sodium Phosphate, *J. Am. Pharm. Assoc. Sci. Ed.* *47*:300-302, 1958.

14. Di Santo, A. R. and Wagner, J. G.: Kinetics of Pharmacologic Response II. Equation for Turnover Time of Goldfish as a Function of Concentration of Ethanol and a Theoretical Derivative Based on a Combination of Occupation and Rate Receptor Theories, *J. Pharm. Sci.* *58*:1077-1085, 1969.

15. Wagner, J. G.: Design and Data Analysis of Biopharmaceutical Studies in Man, *Can. J. Pharm. Sci.* *1*:55-68, 1966.

16. Katchen, B. and Symchowicz, S.: Correlation of Dissolution Rate and Griseofulvin Absorption in Man, *J. Pharm. Sci.* *56*:1108-1110, 1967.

17. Cressman, W. A., Janicki, C. A., Johnson, P. C., Doluisio, J. T. and Braun, G. A.: *In Vitro* Dissolution Rates of Aminorex Dosage Forms and Their Correlation with *in Vivo* Availability, *J. Pharm. Sci.* *58*:1516-1520, 1969.

18. Bates, T. R., Lambert, D. A. and Johns, W. H.: Correlation Between the Rate of Dissolution and Absorption of Salicylamide from Tablet and Suspension Dosage Forms, *J. Pharm. Sci.* *58*:1468-1470, 1969.

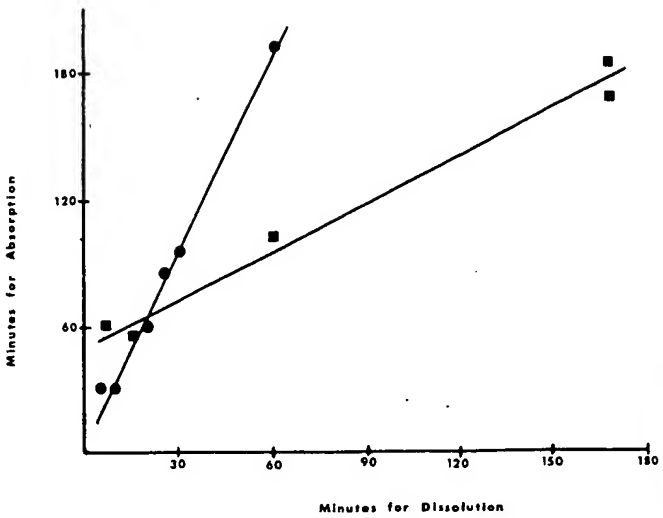


Figure 21.15. Correlation of times required for 25 percent and 50 percent absorption in man (estimated by method of Wagner and Nelson, 1963) with times for 25 percent and 50 percent dissolution *in vitro*. The absorption times were estimated from measurement of total plasma radioactivity following oral administration of various dosage forms of aminorex-C^{14}. Key: ● time for 25 percent absorption *versus* time for 25 percent dissolution; ■ time for 50 percent absorption *versus* time for 50 percent dissolution. From Cressman *et al.* (1969), reproduced with permission of the copyright owner.

Figure 21.16. Correlation between the mean cumulative percent of the dose of salicylamide excreted in the urine of four human volunteers in one hour with the percent salicylamide in solution after 15 mins. (●) and 20 mins (□) *in vitro*. The points from left to right refer to an experimental tablet, a commercial tablet and a commercial suspension of salicylamide. From Bates *et al.* (1969), reproduced with permission of the copyright owner